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71 Applicant: SANDOZ AG, Lichtstrasse 35, CH-4002 Basel
(CH)

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71 Applicant: SANDOZ-PATENT-GMBH,
Humboldtstrasse 3, D-7850 Lörrach (DE)

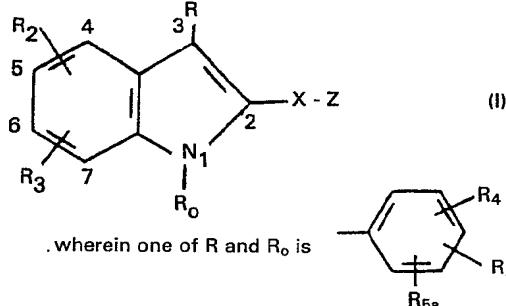
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72 Inventor: Kathawala, Faizulla Gulamhusein,
39 Woodland Avenue, Mountain Lakes, N.J., 07946 (US)

54 Analogs of mevalolactone and derivatives thereof, processes for their production, pharmaceutical compositions containing them and their use as pharmaceuticals.

55 Compounds of formula I

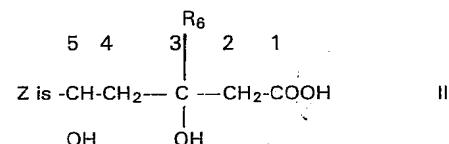


R₄ is hydrogen, R_{5a} must be hydrogen when R₅ is hydrogen, not more than one of R₄ and R₅ is trifluoromethyl, not more than one of R₄ and R₅ is phenoxy and not more than one of R₄ and R₅ is benzyloxy,

R₂ is hydrogen, C₁₋₄alkyl, C₃₋₆cycloalkyl, C₁₋₄alkoxy, (except t-butoxy), trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy,

R₃ is hydrogen, C₁₋₃alkyl, C₁₋₃alkoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy, with the provisos that R₃ must be hydrogen when R₂ is hydrogen, not more than one of R₂ and R₃ is trifluoromethyl, not more than one of R₂ and R₃ is phenoxy, and not more than one of R₂ and R₃ is benzyloxy,

X is -(CH_{2n})₂ or -CH=CH- (n = 0, 1, 2 or 3),



R₄ is hydrogen, C₁₋₄alkyl, C₁₋₄alkoxy, (except t-butoxy), trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy,

R₅ is hydrogen, C₁₋₃alkyl, C₁₋₃alkoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy,

R_{6a} is hydrogen, C₁₋₂alkyl, C₁₋₂alkoxy, fluoro or chloro, and

m is 1, 2, or 3, with the provisos that both R₅ and R_{5a} must be hydrogen when

wherein R₆ is hydrogen or C₁₋₃alkyl in free acid form or in the form of a physiologically-hydrolysable and -acceptable ester or a lactone thereof or in salt form.

These compounds are indicated for use as pharmaceuticals particularly for inhibiting cholesterol biosynthesis and treating atherosclerosis.

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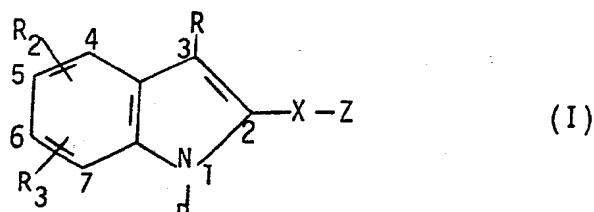
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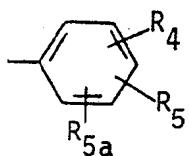
ANALOGS OF MEVALOLACTONE AND DERIVATIVES THEREOF, PROCESSES FOR
THEIR PRODUCTION, PHARMACEUTICAL COMPOSITIONS CONTAINING THEM AND
THEIR USE AS PHARMACEUTICALS

The invention concerns heterocyclic analogs of mevalonolactone and derivatives thereof, processes for their production, pharmaceutical compositions containing them and their use as pharmaceuticals in particular as hypolipoproteinemic and anti-
5 atherosclerotic agents.

The invention is especially concerned with compounds of formula I



wherein one of R and R_0 is  and the other is



primary or secondary C₁-6alkyl, C₃-6cycloalkyl or phenyl-(CH₂)_m-,

wherein R₄ is hydrogen, C₁₋₄alkyl, C₁₋₄alkoxy, (except t-butoxy), trifluoromethyl,

R5 is hydrogen, C₁-3alkyl, C₁-3alkoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy.

R_{5a} is hydrogen, C₁₋₂alkyl, C₁₋₂alkoxy, fluoro or chloro, and

m is 1, 2 or 3,

with the provisos that both R₅ and R_{5a} must be hydrogen when R₄ is hydrogen, R_{5a} must be hydrogen when R₅ is hydrogen, not more than one of R₄ and R₅ is trifluoromethyl, not more than one of R₄ and R₅ is phenoxy and not more than one of R₄ and R₅ is benzyloxy,

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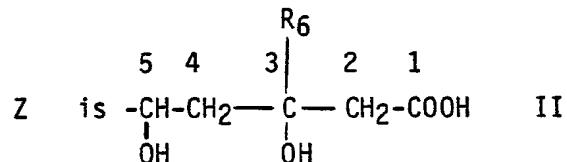
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R₂ is hydrogen, C₁₋₄alkyl, C₃₋₆cyclo-alkyl, C₁₋₄alkoxy, (except t-butoxy), trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy,

R₃ is hydrogen, C₁₋₃alkyl, C₁₋₃alkoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy, with the provisos that R₃ must be hydrogen when R₂ is hydrogen, not more than one of R₂ and R₃ is trifluoromethyl, not more than one of R₂ and R₃ is phenoxy, and not more than one of R₂ and R₃ is benzyloxy,

X is -(CH₂)_n- or -CH=CH- (n=0, 1, 2 or 3),



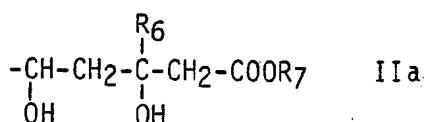
wherein R₆ is hydrogen or C₁₋₃alkyl

25 in free acid form or in the form of a physiologically-hydrolysable and -acceptable ester or a δ lactone thereof or in salt form.

By the term "physiologically-hydrolysable and -acceptable ester" is meant an ester of a compound in accordance with the invention in which the carboxyl moiety is esterified, and which

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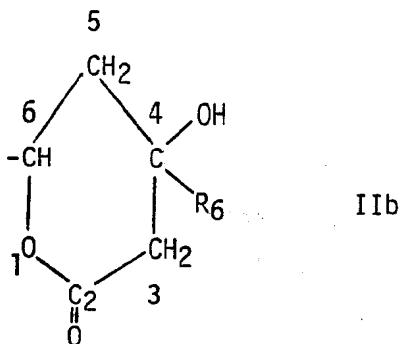
is hydrolysable under physiological conditions to yield an alcohol which is itself physiologically acceptable, e.g. non-toxic at desired dosage levels. Preferred such esters as Z can be represented together with the free acid by formula IIa



5 wherein R₇ is hydrogen, C₁₋₄alkyl or benzyl preferably hydrogen, C₁₋₃alkyl, n-butyl, i-butyl, t-butyl or benzyl and R₆ is as defined above.

When in salt form R₇ represents a cation.

When Z is in lactone form it forms a -lactone of formula IIb

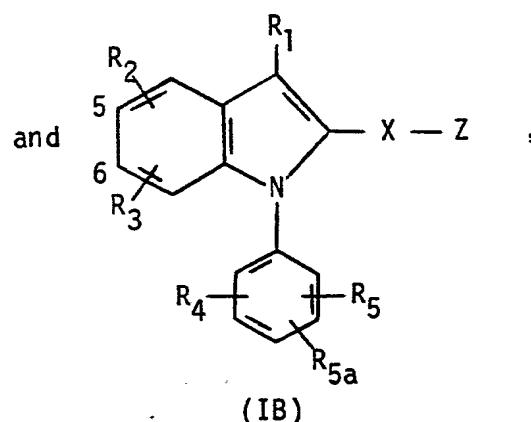
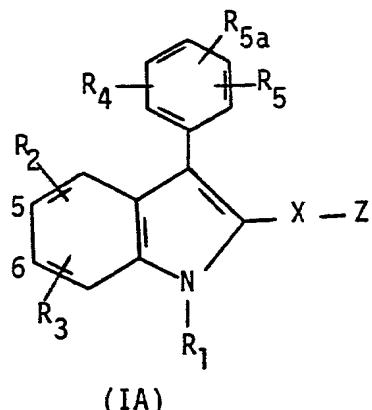


and references to "lactone" hereinafter refer to δ -lactones.

15 Salts of the compounds of the invention, e.g. of the compounds of formula I, include in particular their pharmaceutically acceptable salts. Such pharmaceutically acceptable salts include e.g. alkali metal salts such as the sodium and potassium salts and ammonium salts.

References to compounds of formula I, and sub-species thereof are intended to cover all forms unless otherwise stated.

20 The compounds of formula I may be divided into two groups, the compounds of formula IA and IB:



wherein R₁ is primary or secondary C₁-6alkyl, C₃-6cycloalkyl or phenyl-(CH₂)_m, and R₂-R_{5a}, X, Z and m are as defined above.

The compounds of formula IA may be divided into two sub-groups, the compounds wherein Z is a group of formula II in other than lactone form (Group IAa) and those wherein Z is a group of formula IIb (Group IAb). Likewise, the compounds of formula IB may be divided into two sub-groups, the compounds wherein Z is a group of formula II in other than lactone form (Group IBa) and those wherein Z is a group of formula IIb (Group IBb).

As is self-evident to those in the art, each compound of formula I (and every sub-scope and species thereof) has at least two centers of asymmetry (e.g. the two carbon atoms bearing the hydroxy groups in the group of formula IIa and the carbon atom bearing the hydroxy group and the carbon atom having the free valence in the group of formula IIb) and these lead to four stereoisomeric forms (enantiomers) of each compound (two racemates or pairs of diastereoisomers). These four stereoisomers may be designated as the R,R; R,S; S,R; and S,S enantiomers, all four stereoisomers being within the scope of this invention. Depending

on the nature of substituents further assymetric carbon atoms may be present and the resulting isomers and mixtures thereof also form part of the invention. Compounds containing only two centres of assymetry (four mentioned stereoisomers) are preferred.

5 R_1 is preferably primary or secondary C_{1-6} alkyl not containing assymetric carbon atom (e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, 1-ethylpropyl, neopentyl and n-hexyl), more preferably C_{1-3} alkyl and most preferably methyl, ethyl or i-propyl, especially i-propyl.

10 Alkyl as R_2 is preferably C_{1-3} or n-, i- or t-butyl and alkoxy C_{1-3} or n- or i-butoxy. R_2 is preferably R_2' , where R_2' is hydrogen, C_{1-3} alkyl, C_{1-3} alkoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy, more preferably R_2'' , where R_2'' is hydrogen, C_{1-3} alkyl, methoxy, fluoro, chloro or 4-, 5- or 6-benzyloxy, and most preferably R_2''' , where R_2''' is hydrogen, C_{1-3} alkyl or 4- or 6-benzyloxy, especially hydrogen or methyl and most especially hydrogen.

15 R_3 is preferably R_3' , where R_3' is hydrogen, C_{1-3} alkyl, C_{1-2} alkoxy, fluoro or chloro, more preferably R_3'' , where R_3'' is hydrogen or C_{1-3} alkyl and most preferably R_3''' , where R_3''' is hydrogen or methyl, especially hydrogen. R_3 (R_3' , etc.) must be hydrogen when R_2 (R_2' , etc.) is hydrogen.

20 Preferably, when R_2 (R_2' , R_2'' , etc.) is other than hydrogen and R_3 (R_3' , R_3'' , etc.) is hydrogen, R_2 (R_2' , etc.) is in the 4-, 5- or 6-position.

25 Preferably, when both R_2 (R_2' , R_2'' , etc.) and R_3 (R_3' , R_3'' , etc.) are other than hydrogen, at least one of them is in the 5- or 6-position, neither of them is in the 7-position, and not more than one of them is a member of the group consisting of t-butyl, C_{3-6} cycloalkyl, trifluoromethyl, phenoxy and benzyloxy; more preferably, they are not ortho to each other when neither of them is a member of the group consisting of methyl, methoxy, fluoro and chloro. Most preferably, one is in the 4-position and the other is in the 6-position.

Except where otherwise indicated: (a) Any C₁-4alkyl or C₃-6cycloalkyl group as R₂, R_{2'}, R₃, R_{3'}, etc. is more preferably in the 4- or 6-position. (b) Any C₁-4alkoxy, fluoro or chloro substituent as R₂, R_{2'}, R₃, R_{3'}, etc. is more preferably in the 5-position. (c) Any benzyloxy as R₂, R_{2'}, R₃, R_{3'}, etc. is more preferably in the 4-, 5- or 6-position and most preferably in the 4- or 6-position, especially the 6-position.

Alkyl as R₄ is preferably C₁-3 or n-, i- or t-butyl and alkoxy C₁-3 or n- or i-butoxy. R₄ is preferably R_{4'}, where R_{4'} is hydrogen, C₁-3alkyl, C₁-3alkoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy, more preferably R_{4''}, where R_{4''} is hydrogen, methyl, methoxy, fluoro or chloro, and most preferably R_{4'''}, where R_{4'''} is hydrogen, methyl or fluoro, especially R_{4'''}, where R_{4'''} is hydrogen, 3- or 4-methyl or 4-fluoro and most especially 4-fluoro.

R₅ is preferably R_{5'}, where R_{5'} is hydrogen, C₁-2alkyl, C₁-2alkoxy, fluoro or chloro, more preferably R_{5''}, where R_{5''} is hydrogen, methyl, methoxy, fluoro or chloro, and most preferably R_{5'''}, where R_{5'''} is hydrogen or methyl, especially hydrogen. R₅ (R_{5'}, R_{5''}, etc.) must be hydrogen when R₄ (R_{4'}, R_{4''}, etc.) is hydrogen.

R_{5a} is preferably R_{5a'}, where R_{5a'} is hydrogen or methyl, and most preferably hydrogen. R_{5a} (R_{5a'}, etc.) must be hydrogen when at least one of R₄ (R_{4'}, R_{4''}, etc.) and R₅ (R_{5'}, R_{5''}, etc.) is hydrogen.

Preferably, when R₄ (R_{4'}, R_{4''}, etc.) is other than hydrogen and R₅ (R_{5'}, R_{5''}, etc.) and R_{5a} (R_{5a'}, etc.) are both hydrogen, R₄ (R_{4'}, etc.) is in a meta or para position, more preferably the para position. The most preferred monosubstituted phenyl group is 4-fluorophenyl.

Preferably, when both R₄ (R_{4'}, R_{4''}, etc.) and R₅ (R_{5'}, R_{5''}, etc.) are other than hydrogen and R_{5a} (R_{5a'}, etc.) is hydrogen, at least one of R₄ (R_{4'}, etc.) and R₅ (R_{5'}, etc.) is in a meta or para position (more preferably both are), and not more than one

5 of them is a member of the group consisting of t-butyl, trifluoromethyl, phenoxy and benzyloxy; more preferably, R₄ (R_{4'}, etc.) and R₅ (R_{5'}, etc.) are not ortho to each other when neither of them is a member of the group consisting of methyl, methoxy, fluoro and chloro. The most preferred disubstituted phenyl groups

10 are 3,4- and 3,5-dimethylphenyl and 4-fluoro-3-methylphenyl, especially 3,5-dimethylphenyl and 4-fluoro-3-methylphenyl.

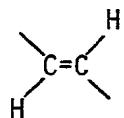
Preferably, when each of R₄ (R_{4'}, etc.), R₅ (R_{5'}, etc.) and R_{5a} (R_{5a'}, etc.) is other than hydrogen, at least two of them (more preferably, all three) are in meta or para positions, and not more than one of them is a member of the group consisting of t-butyl, trifluoromethyl, phenoxy and benzyloxy; more preferably, no two of them are ortho to each other unless at least one member of the each pair of substituents that are ortho to each other is a member of the group consisting of methyl, methoxy, fluoro and chloro. The most preferred trisubstituted phenyl group is 3,5-dimethyl-4-fluorophenyl.

R₆ is preferably R_{6'}, where R_{6'} is hydrogen or C₁₋₂alkyl, more preferably R_{6''}, where R_{6''} is hydrogen or methyl, and most preferably hydrogen.

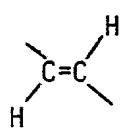
25 R₇ is preferably R_{7'}, where R_{7'} is hydrogen or C₁₋₃alkyl more preferably R_{7''}, where R_{7''} is hydrogen or C₁₋₂alkyl. Such compounds wherein Z is of formula II or IIa are most preferably in salt form. Preferred salt-forming cations are those free from centres of assymetry especially e.g. sodium, potassium or

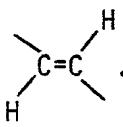
30 ammonium most preferably sodium.

X is preferably X', where X' is $-(CH_2)_m-$ or



, more preferably X", where X" is $-CH_2CH_2-$ or



, especially .

Z is preferably a group of formula IIa wherein R₆ is R_{6'} and

5 R₇ is R_{7'} or a group of formula IIb where in R₆ is R_{6'}, more preferably a group of formula IIa wherein R₆ is R_{6''} and R₇ is R_{7''} or a group of formula IIb wherein R₆ is R_{6''} and most preferably a group of formula IIa wherein R₆ is hydrogen and R₇ is R_{7''} or a group of formula IIb wherein R₆ is hydrogen, especially a group

10 of formula IIa wherein R₆ is hydrogen in salt form particularly in sodium salt form or a group of formula IIb wherein R₆ is hydrogen.

n is preferably m, where m is 1, 2 or 3, preferably 2 or 3 and most preferably 2.

15 Insofar as the compounds of Groups IAa and IBa are concerned, the erythro isomers are generally preferred over the threo isomers, erythro and threo referring to the relative positions of the hydroxy groups in the 3- and 5-positions (of the group of formula II and IIa).

20 As between compounds of formula I having identical R, R₀, R₂, R₃, R₆ and X groups, free acid, salt and ester forms are generally preferred to lactone forms.

The preferred stereoisomers of the compounds having only two assymetric carbons wherein X is a direct bond or $-CH=CH-$, and

25 Z is in other than lactone form are the 3R,5S and 3R,5R isomers and the racemate of which each is a constituent, i.e., the 3R,5S-3S,5R (erythro) and 3R,5R-3S,5S (threo) racemates, with the 3R,5S isomer and the racemate of which it is a constituent being more preferred and the 3R,5S isomer being most preferred.

The preferred stereoisomers of the compounds having only two assymmetric carbons wherein X is $-(CH_2)_m-$, and Z is in other than lactone form are the 3R,5R and 3R,5S isomers and the racemate of which each is a constituent, i.e., the 3R,5R-3S,5S 5 (erythro) and 3R,5S-3S,5R (threo) racemates, with the 3R,5R isomer and the racemate of which it is a constituent being more preferred and the 3R,5R isomer being most preferred.

The preferred stereoisomers of the compounds having only two assymmetric carbons wherein X is a direct bond or $CH=CH-$, and 10 Z is a group of formula IIb are the 4R,6S and 4R,6R isomers and the racemate of which each is a constituent, i.e., the 4R,6S-4S,6R (trans lactone) and 4R,6R-4S,6S (cis lactone) racemates, with the 4R,6S isomer and the racemate of which it is a constituent being more preferred and the 4R,6S isomer being 15 most preferred.

The preferred stereoisomers of the compounds having only two assymmetric carbons wherein X is $-(CH_2)_m-$, and Z is a group of formula IIb are the 4R,6R and 4R,6S isomers and the racemate of which each is a constituent, i.e., the 4R,6R-4S,6S (trans 20 lactone) and 4R,6S-4S,6R (cis lactone) racemates, with the 4R,6R isomer and the racemate of which it is a constituent being more preferred and the 4R,6R isomer being most preferred.

Each of the preferences set forth above applies, not only to the compounds of formula I but also to the compounds of 25 formulae IA and IB and those of Groups IAa, IAb, IBa and IBb as well as to every other subgroup thereof set forth infra, e.g., Groups (i)-(cxiv), unless otherwise indicated. When any preference contains a variable, the preferred significances of that variable apply to the preference in question, unless 30 otherwise indicated.

Preferred groups of compounds of formula I include the compounds

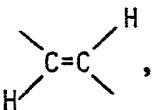
5 (i) of Group IAa wherein R₁ is R_{1'}, R₂ is R_{2'}, R₃ is R_{3'}, R₄ is R_{4'}, R₅ is R_{5'}, R_{5a} is R_{5a'}, R₆ is R_{6'}, R₇ is R_{7'}, and X is X',

10 (ii) of (i) wherein when R_{2'} is other than hydrogen and R_{3'} is hydrogen, R_{2'} is in the 4-, 5- or 6-position; when both R_{2'} and R_{3'} are other than hydrogen, at least one of them is in the 5- or 6-position and neither of them is in the 7-position; when both R_{4'} and R_{5'} are other than hydrogen and R_{5a'} is hydrogen, at least one of R_{4'} and R_{5'} is in a meta or para position; and when each of R_{4'}, R_{5'} and R_{5a'} is other than hydrogen, at least two of them are in meta or para positions,

15 (iii)-(iv) of (i) and (ii) wherein R₆ is R_{6''}, especially hydrogen,

(v)-(vi) of (i) and (ii) wherein R₁ is C₁₋₃alkyl, R₂ is R_{2''}, R₃ is R_{3''}, R₄ is R_{4''}, R₅ is R_{5''}, R₆ is R_{6''}, especially hydrogen, R₇ is R_{7''}, and X is X'',

20 (vii) of (i) wherein R₁ is C₁₋₃alkyl, R₂ is R_{2'''}, R₃ is R_{3'''}, R₄ is R_{4'''}, R₅ is R_{5'''}, R_{5a} is hydrogen, R₆ is

hydrogen, R₇ is R_{7'''}, and X is 

(viii)-(xiii) of (i)-(vi) wherein any salt is a sodium potassium or ammonium salt.

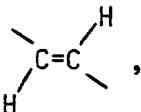
(xiv) of Group IAb wherein R₁ is R_{1'}, R₂ is R_{2'}, R₃ is R_{3'}, R₄ is R_{4'}, R₅ is R_{5'}, R_{5a} is R_{5a'}, R₆ is R_{6'} and X is X',

5 (xv) of (xiv) wherein when R_{2'} is other than hydrogen and R_{3'} is hydrogen, R_{2'} is in the 4-, 5- or 6-position; when both R_{2'} and R_{3'} are other than hydrogen, at least one of them is in the 5- or 6-position and neither of them is in the 7-position; when both R_{4'} and R_{5'} are other than hydrogen and R_{5a'} is 10 hydrogen, at least one of R_{4'} and R_{5'} is in meta or para position; and when each of R_{4'}, R_{5'} and R_{5a'} is other than hydrogen, at least two of them are in meta or para positions,

(xvi)-(xvii) of (xiv) and (xv) wherein R₆ is R_{6''}, especially hydrogen,

15 (xviii)-(xix) of (xiv) and (xv) wherein R₁ is C₁₋₃alkyl, R₂ is R_{2''}, R₃ is R_{3''}, R₄ is R_{4''}, R₅ is R_{5''}, R₆ is R_{6''} especially hydrogen, and X is X'',

(xx) of (xiv) wherein R₁ is C₁₋₃alkyl, R₂ is R_{2'''}, R₃ is R_{3'''}, R₄ is R_{4'''}, R₅ is R_{5'''}, R_{5a} is hydrogen, R₆ is hydrogen,

20 and X is 

(xxi) of Group IBa wherein R₁ is R_{1'}, R₂ is R_{2'}, R₃ is R_{3'}, R₄ is R_{4'}, R₅ is R_{5'}, R_{5a} is R_{5a'}, R₆ is R_{6'}, R₇ is R_{7'}, and X is X',

25 (xxii) of (xxi) wherein when R_{2'} is other than hydrogen and R_{3'} is hydrogen, R_{2'} is in the 4-, 5- or 6-position; when both R_{2'} and R_{3'} are other than hydrogen, at least one of them is in the 5- or 6-position and neither of them is in the 7-position; when both R_{4'} and R_{5'} are other than hydrogen and R_{5a'} is hydrogen, at least one of R_{4'} and R_{5'} is in a meta or para position; and when each of R_{4'}, R_{5'} and R_{5a'} is other than 30 hydrogen, at least two of them are in meta or para positions,

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(xxiii)-(xxiv) of (xxi) and (xxii) wherein R₆ is R₆", especially hydrogen,

5 (xxv)-(xxvi) of (xxi) and (xxii) wherein R₁ is C₁₋₃alkyl, R₂ is R₂", R₃ is R₃", R₄ is R₄", R₅ is R₅", R₆ is R₆", especially hydrogen, R₇ is R₇", and X is X",

(xxvii)-(xxxii) of (xxi)-(xxvi) wherein any salt is a sodium potassium or ammonium salt.

10 (xxxiii) of Group IBB wherein R₁ is R₁', R₂ is R₂', R₃ is R₃', R₄ is R₄', R₅ is R₅', R_{5a} is R_{5a}', R₆ is R₆' and X is X',

15 (xxxiv) of (xxxiii) wherein when R₂' is other than hydrogen and R₃' is hydrogen, R₂' is in the 4-, 5- or 6-position; when both R₂' and R₃' are other than hydrogen, at least one of them is in the 5- or 6-position and neither of them is in the

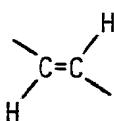
20 7-position; when both R₄' and R₅' are other than hydrogen and R_{5a}' is hydrogen, at least one of R₄' and R₅' is in a meta or para position; and when each of R₄', R₅' and R_{5a}' is other than hydrogen, at least two of them are in meta or para positions,

25 (xxxv)-(xxxvi) of (xxxiii) and (xxxiv) wherein R₆ is R₆", especially hydrogen,

20 (xxxvii)-(xxxviii) of (xxxiii) and (xxxiv) wherein R₁ is C₁₋₃alkyl, R₂ is R₂", R₃ is R₃", R₄ is R₄", R₅ is R₅", R₆ is R₆", especially hydrogen, and X is X",

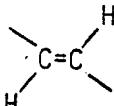
25 (xxxix)-(lxiii) of (i)-(xiii) and (xxi)-(xxxii) wherein the hydroxy groups in the 3- and 5-positions (of the group of formula IIa) have the erythro configuration,

(lxiv)-(lxxxviii) the 3R,5S enantiomers of the compounds of

(xxxix)-(lxiii) wherein X is  and the 3R,5R enantiomers

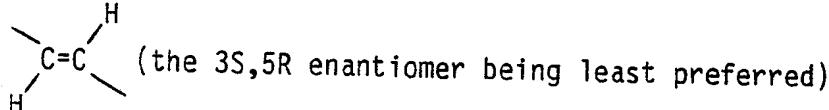
30 of the compounds of these groups wherein X is -(CH₂)_m-,

(lxxxix)-(ci) of (xiv)-(xx) and (xxxiii)-(xxxviii) wherein the hydroxy group on the lactone ring IIb is trans to X (i.e., the trans lactones), and

(cii)-(cxiv) the 4R,6S enantiomers of the compounds of (1xxxix)-(ci) wherein X is  and the 4R,6R

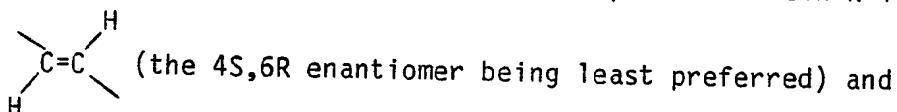
enantiomers of the compounds of these groups wherein X is $-(CH_2)_m-$.

5 Groups (xxxiv)-(1xiii) embrace the 3R,5S-3S,5R racemate and the 3R,5S and 3S,5R enantiomers of the compounds wherein X is



and the 3R,5R-3S,5S racemate and the 3R,5R and 3S,5S enantiomers of the compounds wherein X is $-(CH_2)_m-$ (the 3S,5S enantiomer being least preferred).

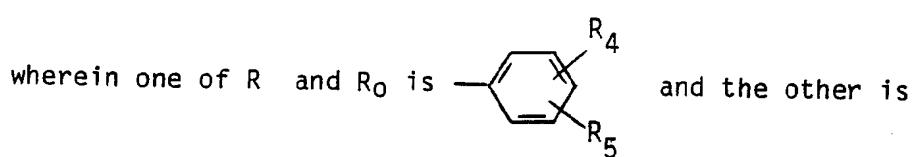
Groups (1xxxix)-(ci) embrace the 4R,6S-4S,6R racemate and the 4R,6S and 4S,6R enantiomers of the compounds wherein X is



15 the 4R,6R-4S,6S racemate and the 4R,6R and 4S,6S enantiomers of the compounds wherein X is $-(CH_2)_m-$, (the 4S,6S enantiomer being least preferred).

In the above mentioned compound groups (i) to (cxiv) those containing a carboxyl group are preferably in salt form with a cation free from asymmetric carbon atoms e.g. sodium, potassium 20 or ammonium especially sodium.

A particular compound group covers those of formula I



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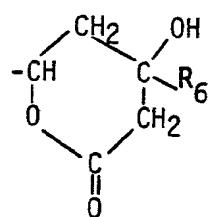
C_1 - 3 alkyl, n-butyl or i-butyl,
 wherein R_4 is hydrogen, C_1 - 3 alkyl, n-butyl,
 i-butyl, C_1 - 3 alkoxy, n-butoxy,
 i-butoxy, trifluoromethyl, fluoro,
 chloro, phenoxy or benzyloxy, and
 R_5 is hydrogen, C_1 - 3 alkyl, C_1 - 3 alkoxy,
 trifluoromethyl, fluoro, chloro,
 phenoxy, or benzyloxy,
 with the provisos that not more
 than one of R_4 and R_5 is trifluoro-
 methyl, not more than one of R_4 and
 R_5 is phenoxy, and not more than
 one of R_4 and R_5 is benzyloxy,

5 R₂ is hydrogen, C₁₋₃alkyl, n-butyl, i-butyl,
C₁₋₃alkoxy, n-butoxy, i-butoxy, trifluoro-
methyl, fluoro, chloro, phenoxy or benzyloxy,
R₃ is hydrogen, C₁₋₃alkyl, C₁₋₃alkoxy, trifluoro-
methyl, fluoro, chloro, phenoxy or benzyloxy,
with the provisos that not more than one of R₂
20 and R₃ is trifluoromethyl, not more than one
of R₂ and R₃ is phenoxy, and not more than one
of R₂ and R₃ is benzyloxy,

X is $-(\text{CH}_2)_n-$ or  ,

wherein n is 0, 1, 2 or 3, and

25 Z is $-\text{CH}(\text{OH})-\text{CH}_2-\text{C}(\text{OH})-\text{CH}_2-\text{COOR}_7'$ or



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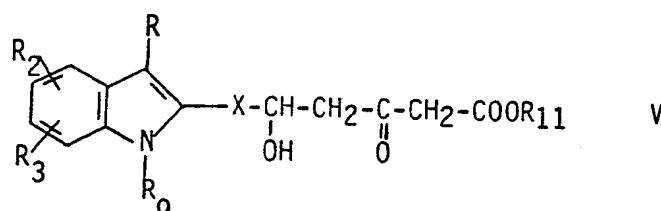
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wherein R_6 is hydrogen or C_{1-3} alkyl, and
 R_7 is hydrogen, C_{1-3} alkyl, n-butyl,
i-butyl, t-butyl, benzyl or M,
wherein M is a pharmaceutically
acceptable cation.

5

The compounds of formula I can be prepared by

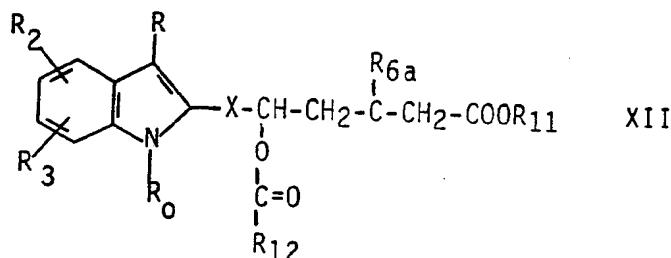
a) when R_6 is hydrogen, reducing a compound of formula V



10

wherein R_{11} is a radical forming a physiologically-hydrolysable and -acceptable ester and X, R, R_0 , R_2 and R_3 are as defined above,

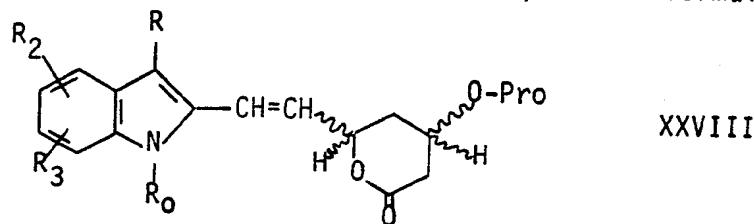
b) when $R_6 = C_{1-3}$ alkyl, hydrolysing a compound of formula XII



15

wherein R_{6a} is C_{1-3} alkyl, R_{12} is an ester forming group and X, R, R_0 , R_3 and R_{11} are as defined above,

c) when X is $-CH=CH-$ deprotecting a compound of formula XXVIII



wherein Pro is a protecting group and R, R₁, R₂ and R₃ are as defined above,

d) hydrolysing a compound of formula I in the form of a physiologically-hydrolysable ester or a lactone or

5 e) esterifying or lactonising a compound of formula I in free acid form,

and when a free carboxyl group is present, recovering the compound obtained in free acid form or in the form of a salt. In processes a) and b) R₁₁ is preferably C₁₋₂alkyl especially methyl and R₁₂ is preferably C₁₋₃alkyl, especially C₁₋₂alkyl, in particular methyl.

10 It will readily be appreciated that the various forms of the compounds of formula I may interconverted as indicated in d) and e) above.

15 In the same way compounds obtained according to a), b), and c) may be hydrolysed to free acid forms and free acid forms may be esterified or lactonised to produce a desired end-product. The invention thus also provides a process for preparing a compound of formula I which comprises hydrolysing a compound of formula I in ester or lactone form or esterifying or lactonising a compound of formula I in free acid form and when a free carboxyl group is present recovering the compound obtained in free acid form or in the form of a salt.

20 25 Unless otherwise stated reactions are performed in a manner conventional for the type of reaction involved. Molar ratios and reaction times are as a rule conventional and non-critical and are chosen according to principles well established in the art on the basis of reactants and conditions employed.

30 35 Solvents, alone or as mixtures, are generally chosen which remain inert and liquid during the reaction in question.

Examples of inert atmospheres are carbon dioxide and more usually nitrogen or a noble gas, nitrogen being preferred. Most reactions, including those wherein use of an inert atmosphere is not mentioned, are carried out in such for convenience.

Reduction according to a) is preferably carried out using a mild reducing agent such as sodium borohydride or, preferably, a complex of t-butylamine and borane in an inert organic solvent such as a lower alkanol, preferably ethanol, conveniently at a 5 temperature of -10° to 30°C, under an inert atmosphere.

Use of an optically pure starting material will lead to only two optical isomers (diastereoisomers) of the resulting end product. However, if stereospecificity is desired it is preferred to utilize a stereoselective reduction in order to maximize 10 production of a mixture of the erythro stereoisomers (racemate) of which the preferred stereoisomer (as set forth above) is a constituent. Stereoselective reduction is preferably carried out in three steps. For example in the first step, the ketoester of formula V is treated with a tri(primary or secondary 15 C₂-4-alkyl)borane, preferably triethylborane or tri-n-butylborane, and air to form a complex. The reaction temperature is suitably 0° to 50°C, preferably 20° to 30°C. The first step is carried out in an anhydrous inert organic solvent, preferably an ether solvent such as tetrahydrofuran, diethyl ether, 1,2-dimethoxyethane or 20 1,2-diethoxyethane, with tetrahydrofuran, being the most preferred solvent. In the second step, for example, the complex is reduced with sodium borohydride, preferably in the same solvent as utilized for the first step, at -100° to -40°C, preferably -90° to -70°C. In the third step, the product of the 25 second step is, for example, treated with, preferably, anhydrous methanol at 20° to 40°C, preferably 20° to 30°C. The amount of methanol is not critical. However, a large excess, e.g., 50-500 moles per mole of ketoester of formula V, is typically utilized.

Hydrolysis according to b) or d) is carried out in a manner 30 conventional for such reactions e.g. employing an inorganic

hydroxide such as NaOH or KOH with, if desired subsequent acidification to give the free acid form. Suitable solvents are mixtures of water and water miscible solvents such as lower alkanols e.g. methanol or ethanol and reaction conveniently takes place at temperatures from 20°C to reflux preferably not more than 80°C. If it is desired to recover the compound in a salt form corresponding to the cation of the hydroxide employed then slightly less than equivalent amounts of the latter may be employed. In b) R₁₂ will conveniently be the same as R₁₁ e.g. C₁₋₃alkyl, especially C₁₋₂alkyl, preferably methyl.

Lactonisation according to e) is carried out in conventional manner e.g. by heating the corresponding acid in an anhydrous inert organic solvent e.g. a hydrocarbon such as benzene, toluene or a xylene or mixtures thereof, preferably at temperatures of 75°C to reflux although more preferably not above 150°C. Preferably, however, a lactonisation agent, e.g. a carbodiimide, preferably a water-soluble carbodiimide such as N-cyclohexyl-N'-(2-(N"-methylmorpholinium)ethyl)carbodiimide p-toluenesulfonate, in an anhydrous inert organic solvent, e.g., a halogenated lower alkane, preferably methylene chloride is employed. Reaction temperatures then lie typically between 10° and 35°C, especially 20° to 30°C.

As is evident to those in the art, a racemic threo 3,5-dihydroxycarboxylic acid yields a racemic cis lactone and a racemic erythro 3,5-dihydroxycarboxylic acid yields a racemic trans lactone. Use of a mixture of threo and erythro 3,5-dicarboxylic acid yields a mixture of cis and trans lactones (all four possible diastereoisomers). Likewise if a single enantiomer of the 3,5-dihydroxycarboxylic acid is utilized, a single enantiomer of the lactone is obtained. For example, lactonisation of a 3R,5S erythro dihydroxycarboxylic acid yields a 4R,6S lactone.

Esterification according to e) is conventional employing e.g. a large excess of a compound R₁₁OH wherein R₁₁ is as defined above at 20°C to 40°C in the presence of a catalytic amount of an

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acid such as p-toluenesulfonic acid. Where methyl esters are required these can also be obtained e.g. using diazomethane in an anhydrous inert ether solvent such as tetrahydrofuran, 1,2-dimethoxyethane or 1,2-diethoxyethane and especially diethyl-ether at e.g. 0° to 30°C preferably 20° to 30°C.

Examples of protecting groups in reaction c) are diphenyl-t-butylsilyl, tri-isopropylsilyl or dimethyl-t-butylsilyl, C₁₋₆n-alkyl, benzyl, triphenylmethyl, tetrahydrofuran-2-yl, tetrahydropyran-2-yl, 4-methoxytetrahydropyran-4-yl, C₁₋₆n-alkanoyloxy. Especially preferred are trisubstituted silyl radicals in particular diphenyl-t-butylsilyl].

Deprotection is carried out in conventional manner e.g. by cleavage under mild conditions such as employing e.g. for removal of a silyl containing group such as diphenyl-t-butylsilyl a fluoride reagent e.g. tetra-n-butyl- ammonium fluoride in an anhydrous inert organic medium preferably tetrahydrofuran containing glacial acetic acid at temperagüres of 20° to 60°C especially 20° to 30°C. Preferably 1-4 moles of fluoride are used per mole of silyl group with 1.2 to 1.8 moles of glacial acetic acid to each mole of fluoride.

The required starting materials may be prepared for example as illustrated in the following reaction schemes. The symbols used are defined as follows

25 R, R_0 , R_1 , R_2 , R_3 , R_4 , R_5 , R_{5a} , R_6 , R_{6a} , R_{11} , R_{12} , X = as defined above.

R_{12a} = C₁₋₃alkyl, preferably C₁₋₂alkyl

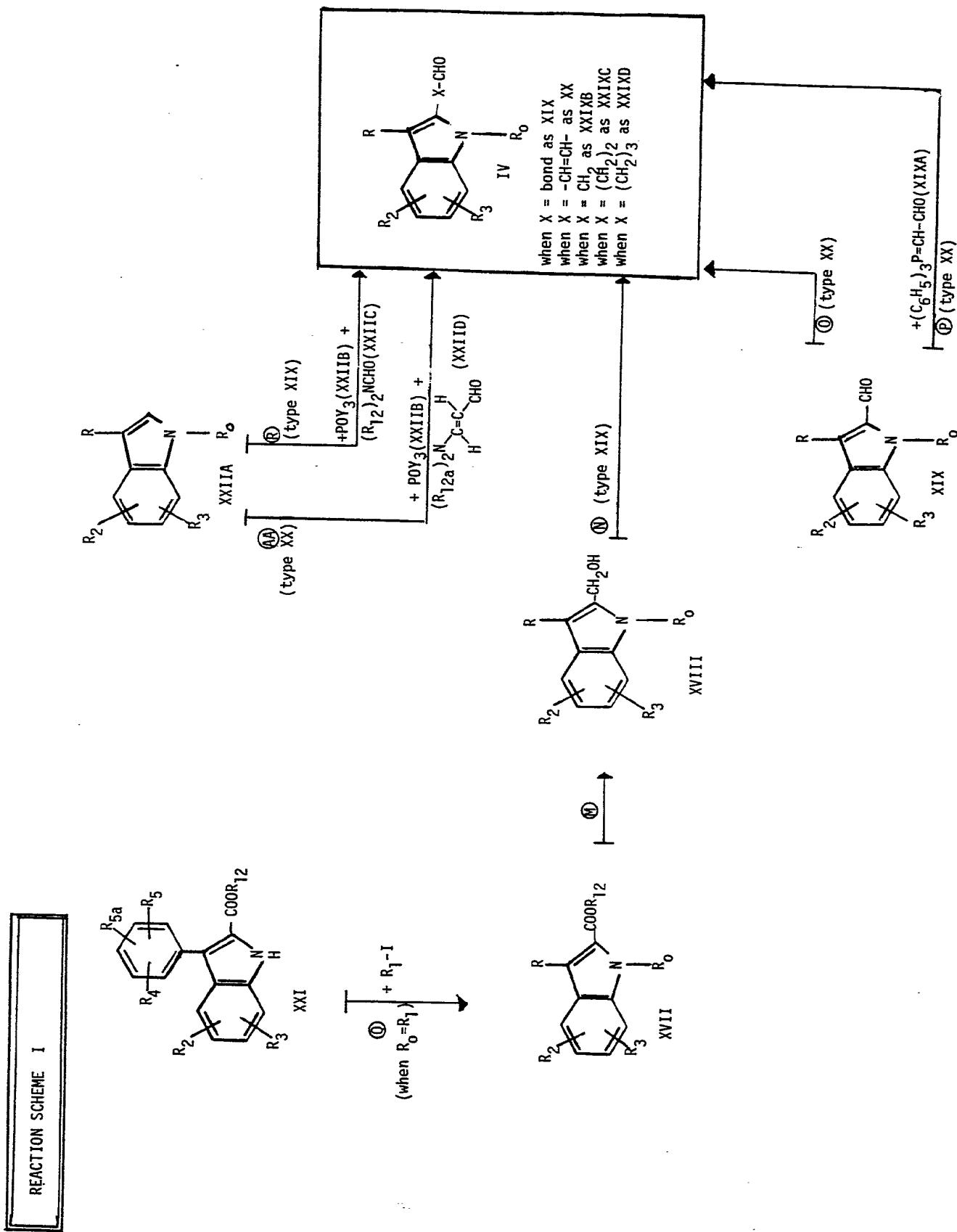
Y = halogen, especially chloro or bromo, preferably chloro

Ac = acetyl

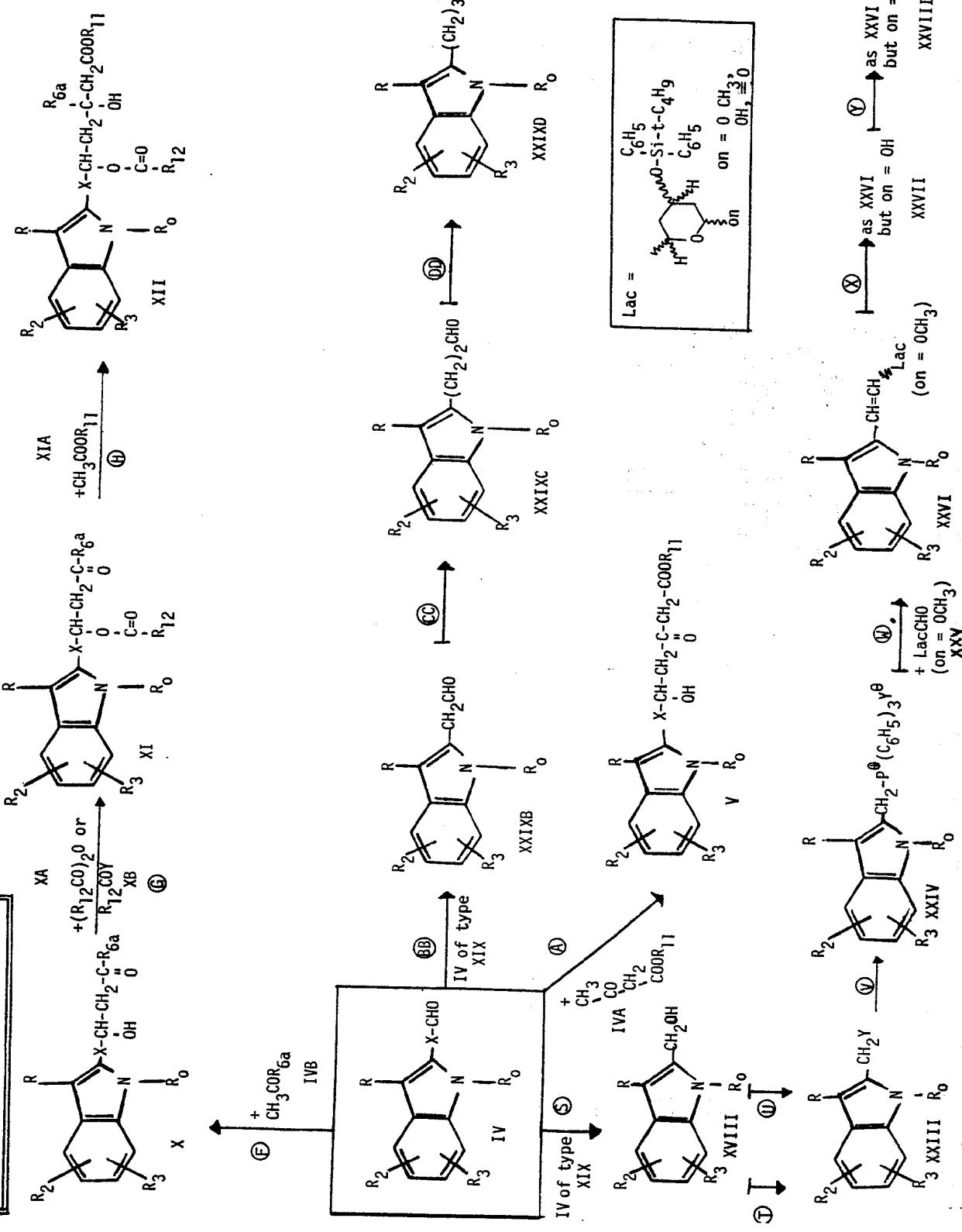
 = phenyl

30 + = t-butyl C_6H_5
 1ac = 

[$\text{On}=\text{OCH}_3$ (XXVI), OH (XXVII) or $=\text{O}$ (XXVIII)]

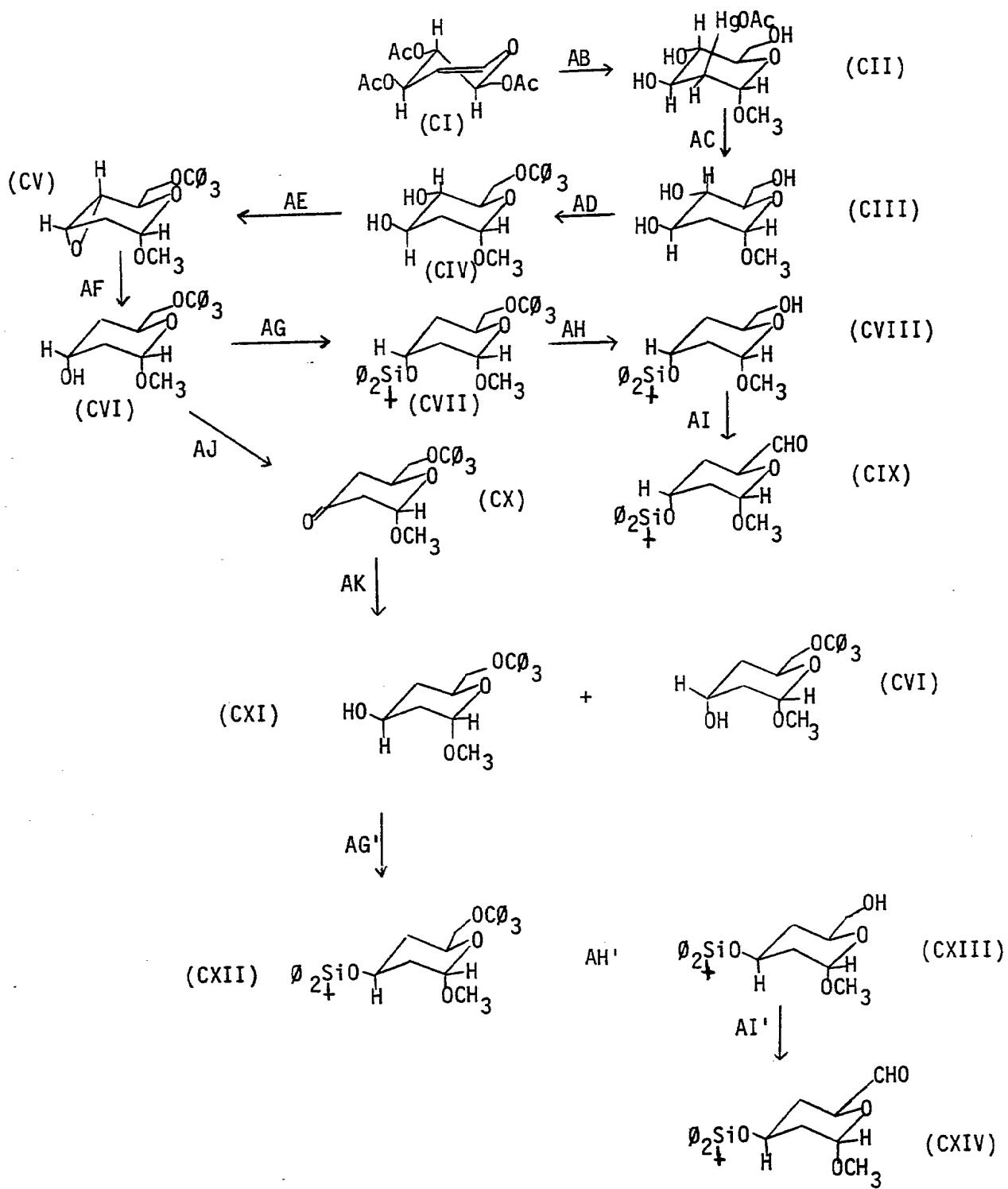


REACTION SCHEME II



Reaction Scheme III

Two isomers of the compound of formula XXV may be synthesized by the following series of reactions:



Unless otherwise stated reactions are performed in a manner conventional for the type of reaction involved. Mol ratios and reaction times are as a rule conventional and non-critical and are chosen according to principles well established in the art on the basis of reactants and conditions employed.

Solvents, alone or as mixtures, are generally chosen which remain inert and liquid during the reaction in question.

Examples of inert atmospheres are carbondioxide and more usually nitrogen, helium, neon, argon or krypton, nitrogen being preferred. Most reactions, including those wherein use of an inert atmosphere is not mentioned are carried out in such for convenience.

The following tables give examples of typical reaction conditions in reaction schemes I and II temperatures are in degrees centigrade.

Abbreviations

THF (tetrahydrofuran)

DMF (dimethylformamide)

Reaction	Type/Steps	Special conditions/ Reagents	Temperatures	Atmosphere	Solvents
Ⓐ	1. IVA + base 2. add IV	1. Strong base e.g. n-buty l lithium for dianion, lith ium diisopropylamide and NaH (latter for generation of monoanion only). pref. NaH for monoanion then nBuLi	-80° to 10° esp. -20° to 5°	inert gas	anhydrous THF, diethyl ether, 1,2- dimethoxy-, 1,2- diethoxy-ethane
Ⓔ	1. IVB + base 2. add IV	1. Strong base as Ⓛ preferred lithium diiso- propylamide. Mol ratio of IVB to IV esp. 3:1	-80° to -40° esp. -80° to -75°	inert gas	as Ⓛ
Ⓖ	acylation	base e.g. pyridine, ter tiary amine such as tri methylamine, 4-dimethyl- aminopyridine	10° to 50° esp. 20° to 30°	inert gas	excess pyridine and/or ether e.g. THF
Ⓗ	1. XIIA + base (cf. Ⓛ) 2. add XI	reagents as Ⓛ Mol ratio of XIIA to XI esp. 3:1	1. -80° to 0° 2. -80° to -40° esp. -80° to -70°	inert gas	as Ⓛ esp. THF
Ⓜ	reduction	metal hydride e.g. lithium aluminium hydride diisobutyl aluminium hydride	-80° to reflux pref. <70° esp. -80° to 25°		as Ⓛ esp. THF
Ⓝ	mild oxidation	e.g. MnO ₂ in large molar excess	20° to reflux pref. <80°		as Ⓛ
Ⓞ	1. cis-1-lithium-2- ethoxyethylene* 2. p-TsOH	1. p-toluenesulfonic acid in catalytic amounts	1. -80° to -40° esp. -80° to -70°	1. inert gas 2. THF + water	1. anhyd. THF 2. THF + water

* prepared e.g. as
described in the
examples.

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Reaction	Type/Steps	Special conditions/ Reagents	Temperatures	Atmosphere	Solvents
⑥	Wittig	those usual for Wittig reactions	-20° to reflux pref. < 140°	inert gas	as ④ or anhyd. hydrocarbon e.g. benzene, toluene
⑦	1. XXI + base 2. R ₁ -I	1. base e.g. as ④ esp. NaH 2. R ₁ -I	1. -20° to 30° 2. -15° to reflux pref. < 80° esp. 20-30°	inert gas	as ④ or anhyd. diethylacetamide and esp. dimethyl acetamide
⑧**	Vilsmeier-Haack	1. Phosphorous oxychloride is pref. as XXIIC 2. XXIIA + iminium salt from 1 3. add base	1. 0° to 35° esp. 0° to 15° 2. 60° to 120° esp. 80° to 105° 3. 10° to 45° esp. 10°-25°	1. inert gas 2. " " " " " " " " " " " "	1. and 2. anhyd. excess XXIIC alone or with lower alkynitrile e.g. acetonitrile
⑨	reduction	as ⑩ pref. NaBH ₄	-5° to 35°	inert gas	as ④ or pref. when using NaBH ₄ ether + lower alkanol e.g. THF + methanol
⑩	halogenation	phosphorous trihalide, thionylhalide or oxallyl halide (halide = Y) + optionally a trace of DMF	20° to 35° for phosphorous tri- halide, otherwise -10° to 20° esp. -10° to 5°	inert gas	diethylether or THF
⑪	halogenation	triphenylphosphine + CY ₄	-10° to reflux pref. < 150° when run in excess CY ₄ 25° to reflux < 100°		excess CY ₄ or as ⑪

** Mol ratio 1. 1-5 of XXIIB + 1 of XXIIC : 1 of XXIIA
3. >4 pref. 4 to 6 of base per 1 of XXIIB in first step

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Reaction	Type/Steps	Special conditions/ Reagents	Temperatures	Atmosphere	Solvents
⑤		triphenylphosphine	60° to reflux pref. < 150° esp. 100°-110°	inert gas	anhydr. hydro- carbon e.g. benzene, toluene or a xylene
⑥	1. Wittig Reaction 2. base XXV	1. as ④ 2. produces mixture of cis(Z) and trans(E) which can be separated here (conventionally) or further reacted and separated at a later stage	1. 0° to 25° 2. -10° to reflux pref. < 80° esp. 20° to 30°	inert gas	1. + 2. as ④
⑦	hydrolysis	acid e.g. 10% HCl in THF or glacial CH ₃ COOH in THF/H ₂ O Reaction produces some "6"-epimerisation which is greater if HCl is used (pref. is glacial CH ₃ COOH/ THF/H ₂ O: 3/2/1)	10° to 100° esp. 60°	THF with water	
⑧	oxidation (cf. Tetrahedron Letters 1976, pp. 2503-6)	a) mild conditions e.g. N-methylmorpholine oxide + dichlorotris((C ₆ H ₅) ₃ P)- ruthenium II or e.g. b) AgCO ₃ on celite	a) 0° to 40° pref. 20° to 30° b) 0° to reflux pref. < 150° esp. 100° to reflux	inert gas	a) anhydrous DMF, acetone b) as ⑤
⑨	cf. ⑧	1. XXIB + XXID 2. XXIA + iminium salt from 1. 3. add base	1. - 10° to 25° esp. -10° to 5° 2. 60° to 100° esp. 65° to 85° 3. 20° to 45° esp. 20° to 30°	inert gas	as ⑧

Reaction	Type/Steps	Special conditions/ Reagents	Temperatures	Atmosphere	Solvents
⑥B ⑦C ⑧D	Wittig	Successive Wittig reactions as ⑧ employing e.g. $(C_6H_5)_3P^{\oplus}-CH_2-OCH_3$ Cl [⊖] (XXIXA) e.g. firstly XXIXA + strong base secondly add aldehyde thirdly hydrolyse	cf. ⑧	cf. ⑧	cf. ⑧

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CI is the commercially available compound tri-*O*-acetyl-*D*-glucal.

The preferred reactions conditions for Reactions AB-AI are:

AB: (1) sodium, methanol, 20°C, 15 minutes; (2) mercuric acetate, 25°C.

5 AC: sodium chloride, sodium borohydride, methanol + isopropanol, 20°C.

AD: triphenylmethyl chloride, pyridine, 35°C.

AE: (1) sodium hydride, tetrahydrofuran, 20°C, (2)

1-(2',4',6'-triisopropylbenzenesulfonyl)imidazole, -30°-20°C.

10 AF: lithium aluminium hydride, methyl *t*-butyl ether, -10°C.

AG: *t*-butyldiphenylchlorosilane, imidazole, N,N,dimethyl-formamide, 20°C.

AH: 70% aqueous trifluoroacetic acid, methylene chloride, -80° to -50°C especially -55°C rising over 1 hour to -10° to +10°

15 esp. -10° to 0°, and keeping at latter for 3-5 hours Epimerisation can be minimized by employing low temperatures and/or short times and terminating the reaction before completion.

AI: pyridinium chlorochromate or especially chromium trioxide (e.g. as Collins oxidation) in molar excess (e.g. 6 mole per

20 mole of CVIII)/pyridine, pyridine, methylene chloride, 20°-30°C.

AJ: oxidation cf. AI.

AK: reduction cf. a) and S above especially NaBH₄.

25 Resulting compounds may be conventionally separated (e.g. HPLC or column chromatography) or directly further reacted.

The compounds of formulae IVA, IVB, XA, XB, XIA, XVII, XIXA, XXI, XXIIA-XXIID, XXIXA and CI and the reagents not

designated by a Roman numeral are known or, if unknown, may be synthesized by processes analogous to those described in the

30 literature for similar known compounds. As for the compound of formula XXV, one isomer is disclosed in Yang et al., Tetrahedron Letters 23, 4305-4308 (1982), another is disclosed in Reaction Scheme III and the synthesis of a third isomer is disclosed in Reaction Scheme III.

The isomer of Yang et al. and the isomer disclosed in Reaction Scheme III yield lactones having the 4R,6S configuration and, as a result of epimerization in Reaction X, such compounds having the 4R,6R configuration. Lactones having the 4S,6R and 4S,6S configuration may be obtained from the other isomer whose synthesis is disclosed in Reaction Scheme III.

The availability of these intermediates enables synthesis of optically pure end products.

Reaction products both intermediate and final can be isolated and purified in conventional manner whereby intermediates can where appropriately be employed directly in a subsequent reaction

Mixtures of stereoisomers (cis, trans and optical) may be separated by conventional means at whatever stage of synthesis is appropriate. Such methods include re-crystallisation, chromatography, formation of esters with optically pure acids and alcohols or of amides and salts (cf also Sommer et al. J.A.C. S 80, 3271 (1958)) with subsequent reconversion under retention of optical purity. For example diastereoisomeric (-)- α -naphthyl-phenylmethylsilyl derivatives of a lactone type end product of formula I may be separated on a silica column having covalently bound L-phenylglycine (eluant n-hexane/acetate : 1/1).

Salts may be prepared in conventional manner from free acids, lactones and esters and vice-versa. Whilst all salts are covered by the invention pharmaceutically acceptable salts especially sodium, potassium and ammonium particularly sodium salts are preferred.

The various forms of the compounds of formula I are by virtue of their interconvertability useful as intermediates in addition to the use set out below.

Also within the scope of this invention are the intermediates of formulae V, X, XI, XII, XX, XXIV, XXVI-XXVIII and XXIXB-XXIXD. The preferences for each variable are the same as those set forth for the compounds of formula I, with the preferred groups of such compounds including those that correspond to Groups (i)-(xiii) and (xxxix)-1xxxviii) (for

formulae V, X-XII, XX and XXIXB-XXIXD) and Groups (xiv)-(xx), (xxxiii)-(xxxviii) and (lxxxix)-(cxiv) for formulae XXVI-XXVIII) to the extent consistent therewith.

5 The compounds of formula I possess pharmacological activity in particular they are inhibitors of 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase and as a consequence inhibitors of cholesterol biosynthesis as demonstrated in the following three tests.

10 Test A: In Vitro Microsomal Assay of HMG-CoA Reductase Inhibition:

15 200 ul. aliquots (1.08-1.50 mg./ml.) of rat liver microsomal suspensions, freshly prepared from male Spargue-Dawley rats (150-225 g. body weight), in Buffer A with 10 mmol. dithiothreitol are incubated with 10 ul. test substance dissolved in dimethylacetamide and assayed for HMG-CoA reductase activity as described by Ackerman et al., J. Lipid Res. 18, 408-413 (1977). In the assay the microsomes are the source of the HMG-CoA reductase enzyme which catalyses the reduction of HMG-CoA to mevalonate. The assay employs a chloroform extraction to separate the product, [¹⁴C]mevalonolactone, formed by the HMG-CoA reductase reaction from the substrate, [¹⁴C]HMG-CoA. [³H]mevalono-lactone is added as an internal reference. Inhibition of HMG-CoA reductase is calculated from the decrease in specific activity [¹⁴C/³H]mevalonate) of test groups compared to controls.

25 Test B: In Vitro Cell Culture Cholesterol Biosynthesis Screen:

30 The cell culture is prepared as follows: Stock monolayer cultures of the Fu5AH rat hepatoma cell line (originally obtained from G. Rothblat; see Rothblat, Lipids 9, 526-535 (1974) are routinely maintained in Eagle's Minimum Essential Medium (EMEM) supplemented with 10% fetal bovine serum (FBS) in 75 cm² tissue culture flasks. For these studies, when the cultures reach

confluence, they are removed by mild enzymatic treatment with 0.25% trypsin in Hanks' balanced salt solution (without calcium and magnesium). After centrifugation of the cell suspension and aspiration of the enzymatic solution, a cell pellet is

5 resuspended in an appropriate volume of media for seeding into 60 mm. tissue culture dishes. The cultures are incubated at 37°C in an atmosphere of high humidity and 5% carbon dioxide. When the cultures are confluent (approximately 5 days), they are ready for use. The culture media is aspirated from the dishes and

10 replaced with 3 ml of EMEM supplemented with 5 mg/ml of dilipidized serum protein (DLSP) prepared by the method of Rothblat et al., *In Vitro* 12, 554-557 (1976). Replacement of the FBS with DLSP has been shown to stimulate the incorporation of [¹⁴C]acetate into sterol by removing the exogenous sterol

15 supplied by the FBS, thereby requiring the cells to synthesize sterol. Enhanced 3-hydroxy-3-methylglutaryl Coenzyme A reductase (HMG-CoA reductase) activity is measurable in the cells in response to the lack of exogenous sterol. Following approximately 24 hours incubation at 37°C in the DLSP supplemented media, the

20 assay is initiated by the addition of 3 μ Ci of [¹⁴C]acetate and the test substances solubilized in dimethylsulfoxide (DMSO) or distilled water. Solvent controls and compactin-treated controls are always prepared. Triplicate 60mm. tissue culture dishes are run for each group. After 3 hours incubation at 37°C, the

25 cultures are examined microscopically using an inverted phase contrast microscope. Notations are made of any morphological changes which may have occurred in the cultures. The media is aspirated and the cell layer is gently washed twice with 0.9% sodium chloride solution (saline). The cell layer is then

30 harvested in 3 ml. of 0.9% saline by gentle scraping with a rubber policeman and transferred to a clean glass tube with Teflon lined cap. The dishes are rinsed with 3 ml. of 0.9% saline and rescraped, and the cells are combined with the first harvest. The tubes are centrifuged at 1500 r.p.m. for 10 minutes

in an IEC PR-J centrifuge, and the supernatant is aspirated.

The cells are then extracted as follows: One ml. of 100% ethanol is added to the cell pellet followed by sonication for 10 seconds with a "LO" setting of 50 on a Bronwell Biosonik IV. One 5 hundred ul. are taken for protein determination. One ml. of 15% potassium hydroxide (KOH) is added, and the samples are thoroughly vortexed. Saponification is accomplished by heating the ethanol-KOH treated samples at 60°C for 60 minutes in a water bath. Following dilution of the samples with 2ml. of distilled 10 water, they are extracted three times with 7 ml. of petroleum ether. The petroleum ether extracts are then washed three times with 2 ml. of distilled water and finally taken to dryness under a stream of nitrogen.

15 The obtained samples are then analyzed by thin layer chromatography (TLC) as follows: Residues from the petroleum ether extraction are taken up in a small volume of hexane and spotted on silica gel 60 TLC plates (E. Merck). Development of the plates is carried out in a 150 parts by volume hexane: 50 parts by volume diethyl ether: 5 parts by volume glacial acetic 20 acid solvent system using a three phase development procedure. Visualization is accomplished in an iodine vapor chamber. The plates are divided into five sections such that each section contains the molecules having the following approximate Rf values: section 1- 0-0.4, section 2- 0.4-0.55, section 3- 25 0.55-0.7, section 4- 0.7-0.9 and section 5- 0.9-1.0. Section 2 contains the non-saponifiable sterols. The five sections of the TLC plates are scraped into scintillation vials. Blanks are also prepared from scrapings of chromatographed non-labelled standards. ACS[®] scintillation cocktail is added, and the 30 radioactivity is determined in a liquid scintillation spectrometer. [¹⁴C]hexadecane standards are used to determine counting efficiencies. The total protein content of the samples is determined employing the Bio-Rad Protein Assay System.

The results are reported as disintegrations per minute per mg protein (d.p.m./mg protein) for each of the live TLC sections. Mean d.p.m./mg protein \pm standard error of the mean are compared for percentage change (% Δ) and statistical significance with 5 solvent control means. TLC section 2 data is taken as a measure of HMG-CoA reductase activity inhibition.

Test C: In Vivo Cholesterol Biosynthesis Inhibition Tests: In vivo studies utilize male Wistar Royal Hart rats weighing 150 \pm 20 g which have been kept for 7-10 days on an altered light 10 cycle (6:30 a.m. - 6:30 p.m. dark) housed two per cage and fed powdered Purina Rat Chow and water ad libitum. Three hours before the diurnal maximum of cholesterol synthesis at mid-dark, the rats are administered the test substances dissolved or as a 15 suspension in 0.5% carboxymethylcellulose in a volume of 1 ml/100 g body weight. Controls receive vehicle alone. One hour after receiving the test substance, the rats are injected 20 intraperitoneally with about 25 μ Ci/100 g body weight of sodium [1- 14 C]acetate 1-3 mCi/mmol. Two hours after mid-dark, blood samples are obtained under sodium hexobarbital anesthesia and the 25 serum separated by centrifugation.

Serum samples are saponified and neutralized, and the 3 β -hydroxy sterols are precipitated with digitonin basically as described by Sperry et al., J. Biol. Chem. 187, 97 (1950). The [14 C]digitonides are then counted by liquid scintillation 25 spectrometry. After correcting for efficiencies, the results are calculated in nCi (nanocuries) of sterol formed per 100 ml of serum. Inhibition of sterol synthesis is calculated from the reduction in the nCi of sterols formed from test groups compared to controls.

30 The compounds are thus indicated for use as hypolipoproteinemic and anti-atherosclerotic agents.

An indicated suitable daily dosage for use in the treatment of hyperlipoproteinemia and atherosclerosis is from about

1 to 2000 mg preferably 1.5 to 100 mg suitably administered in divided dosages of 0.25 to 1000 mg preferably 0.4 to 50 mg two to four times daily or in retard form.

They may be administered in free acid form or in the form 5 of a physiologically-hydrolysable and -acceptable ester or a lactone thereof or in pharmaceutically acceptable salt form whereby the various forms have activities in the same range.

The invention therefore also concerns a method of treating hyperlipoproteinemia or atherosclerosis by administration of a 10 compound of formula I in free acid form or in the form of a physiologically-hydrolysable and -acceptable ester or a lactone thereof or in pharmaceutically acceptable salt form as well as such compounds for use as pharmaceuticals e.g. as hypolipoproteinemic and anti-atherosclerotic agents.

15 The compounds may be administered alone, or in admixture with a pharmaceutically acceptable diluent or carrier, and, optionally other excipients, and administered orally in such forms as tablets, elixirs, capsules or suspensions or parenterally in such forms as injectable solutions or 20 suspensions.

The preferred pharmaceutical compositions from the stand-point of ease of preparation and administration are solid compositions, particularly tablets and hard-filled or liquid-filled capsules.

25 Such compositions also form part of the invention.

The following examples, in which all temperatures are in °C illustrate the invention.

EXAMPLE 1

Methyl (E)-3,5-dihydroxy-7-[3'-(4"-fluorophenyl)-1'-methylindol-2'-yl]hept-6-enoate (Compound no. 1)

a) Ethyl 3-(4'-fluorophenyl)-1-methylindole-2-carboxylate

5 (Reaction Q; compound XVIIa)

To a solution of 8.0 g (28 mmol) of ethyl 3-(4'-fluorophenyl)indole-2-carboxylate in 30 ml of dry dimethylacetamide stirred under nitrogen at -10°, 1.6 g (33 mmol) of sodium hydride is added. The reaction mixture is stirred at -10° under nitrogen for 45 minutes, 4.8 g (32 mmol) of methyl iodide is added at -10°, and the reaction mixture is allowed to warm to room temperature and stirred under nitrogen at room temperature for 2 hours. The reaction mixture is poured into 400 ml of ice/water, neutralized with 4 ml of 2N. hydrochloric acid and extracted several times with diethyl ether. The diethyl ether extracts are combined, washed with water, washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered and evaporated at reduced pressure. The residue is purified by column chromatography utilizing a silica gel column and chloroform as the eluant. The fractions containing the product are combined and evaporated at reduced pressure, and the residue is crystallized from *n*-hexane/petroleum ether to obtain the product, m.p. 61-62°.

25 b) 3-(4'-Fluorophenyl)-2-hydroxymethyl-1-methylindole
(Reaction M; compound XVIIIa)

To a solution of 20.0 g (67 mmol) of compound XVIIa in 500 ml of dry tetrahydrofuran stirred at -78° under nitrogen, 80 ml of 25% (by weight) diisobutylaluminum hydride/toluene is added, and the reaction mixture is stirred at -78° under nitrogen for 4 hours. The reaction mixture is allowed to warm to -10°, an additional 30 ml of 25% (by weight) diisobutylaluminum hydride/toluene is added, the reaction mixture is stirred at 0° under nitrogen for an additional 3 hours, a further 30 ml of 25% (by

weight) diisobutylaluminum hydride/toluene is added, and the reaction mixture is stirred at 0° under nitrogen for a further 1 hour. The reaction mixture is treated with saturated ammonium chloride solution and filtered, and the organic layer is 5 separated, dried over anhydrous magnesium sulfate, filtered and evaporated at reduced pressure. The residue is triturated with n-hexane to obtain the product, m.p. 99°-104°.

c) 3-(4'-Fluorophenyl)-1-methylindole-2-carboxaldehyde
(Reaction N; compound IVa)

10 A mixture of 17.0 g (67 mmol) of compound XVIIIa, 90.0 g (1.03 mol) of manganese dioxide and 1.2 l of anhydrous diethyl ether is stirred at room temperature under nitrogen for 14 hours. The reaction mixture is filtered, and the diethyl ether is evaporated at reduced pressure. The residue is flash 15 chromatographed on a silica gel column using methylene chloride as the eluant, the fractions containing the product are combined and evaporated at reduced pressure, and the residue is triturated with n-pentane to obtain the product, m.p. 75°-79°.

d) (E)-3-[3'-(4"-Fluorophenyl)-1'-methylindol-2'-yl]propen-
20 aldehyde (Reaction O; compound IVb)

25 25 ml of 1.7M. n-butyl lithium/n-hexane (42 mmol) is added dropwise to a solution of 14.5 g (40 mmol) of tri-n-butylstannyl-vinylethoxide in 600 ml of dry tetrahydrofuran stirred at -78° under nitrogen, stirring is maintained for 2 hours under the same 25 conditions, and 9.0 g (35.6 mmol) of compond IVa dissolved in 60 ml of dry tetrahydrofuran, is added rapidly dropwise. The reaction mixture is stirred at -78° under nitrogen for 3.5 hours, quenched with 60 ml of saturated ammonium chloride solution and extracted several times with diethyl ether. The diethyl ether 30 extracts are combined, washed with water, washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered and evaporated at reduced pressure. The residue is partitioned between n-hexane and acetonitrile (to remove the organotin compounds), and the acetonitrile layer is

evaporated at reduced pressure to obtain an oil. The oil is dissolved in 300 ml of tetrahydrofuran, 50 ml of water and 30 mg of p-toluenesulfonic acid monohydrate are added, and the reaction mixture is stirred for 2 hours at room temperature and then extracted several times with diethyl ether. The diethyl ether extracts are combined, washed with water, washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered and evaporated to dryness at reduced pressure. The residue is triturated with n-hexane/diethyl ether to obtain the product, m.p. 110°112°. A subsequent batch melted at 115-118°.

10 e) Methyl (E)-7-[3'-(4"-fluorophenyl-1'-methylindol-2'-yl]-5-hydroxy-3-oxohept-6-enoate (Reaction A; compound Va)

15 3.5 ml (32.4 mmol) of methyl acetoacetate is added dropwise to a suspension of 1.6 g of 50% (by weight) sodium hydride (33.3 mmol) in 400 ml of dry tetrahydrofuran stirred at -15° under nitrogen. The reaction mixture is stirred at -15° under nitrogen for 20 minutes, 19 ml of 1.7M. n-butyl lithium/n-hexane (31.9 mmol) is added, the reaction mixture is stirred at -15° under nitrogen for 20 minutes, a solution of 5.3 g (19 mmol) of compound IVb in 100 ml of dry tetrahydrofuran is added, and the reaction mixture is stirred at -15° under nitrogen for 30 minutes. The reaction mixture is quenched with dilute hydrochloric acid and extracted several times with diethyl ether. The diethyl ether extracts are combined, washed with water, washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered and evaporated to dryness at reduced pressure. The residue is triturated with n-pentane (to remove excess methyl acetoacetate) to obtain the crude product as an oil.

20 25 30 The product is a racemate that may be resolved into its d and l components.

f) Methyl (E)-3,5-dihydroxy-7-[3'-(4"-fluorophenyl)-1'-methylindol-2'-yl]-hept-6-enoate (process a); compound no. 1)

2.0 g of borane-t-butylamine complex is added to a solution of 8.0 g (20.2 mmol) of crude racemic compound Va in 200 ml of absolute ethanol stirred at 0° under nitrogen. The reaction mixture is stirred at 0° under nitrogen for 3 hours, and saturated sodium chloride solution is added. The reaction mixture is acidified with dilute hydrochloric acid and extracted several times with diethyl ether. The diethyl ether extracts are combined, washed with water, washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered and evaporated to dryness at reduced pressure. The obtained oil is purified by flash chromatography using a silica gel column and 1:1 ethyl acetate/chloroform as the eluant. The product, a mixture of four stereoisomers, is obtained as a yellow oil.

The obtained mixture of stereoisomers (erythro and threo) may be separated by conventional means into two racemic mixtures each of which may be resolved into two optically pure enantiomers. The four isomers may be designated as the 3R,5R, 3S,5S, 3R,5S and 3S,5R isomers. Preferred are the 3R,5R and 3R,5S isomers and the racemate of which each is a constituent, viz., the 3R,5R-3S,5S and the 3R,5S-3S,5R racemate.

EXAMPLE 2

(E)-3,5-Dihydroxy-7-[3'-(4"-fluorophenyl)-1'-methylindol-2'-yl]-hept-6-enoic acid (process d)/ester hydrolysis; compound no. 3)

2.8 ml of 1N. aqueous potassium hydroxide (2.8 mmol) is added to a solution of 1.1 g (2.77 mmol) of compound no. 1 in 100 ml of 95% aqueous methanol stirred at room temperature, and the reaction mixture is stirred at room temperature for 3 hours. The solvent is evaporated at reduced pressure, the residue [crude potassium salt (compound 2) a mixture of four stereoisomers] is dissolved in water, and the aqueous

solution is extracted with diethyl ether. The aqueous phase is acidified with dilute hydrochloric acid (pH 6.0) and extracted several time with diethyl ether. The diethyl ether extracts are combined, washed with water, washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered and evaporated at reduced pressure to give the crude product as a yellow oil. It is a mixture of four stereoisomers.

If desired, potassium salt or free acid (compound no. 3) may be separated into two racemic mixtures (erythro, threo) each of which may be resolved into two optically pure enantiomers. The four stereoisomers may be designated as the 3R,5R, 3S,5S, 3R,5S and 3S,5R isomers. Preferred are the 3R,5R and 3R,5S isomers and the racemate of which each is a constituent, viz., the 3R,5R-3S,5S racemate and the 3R,5S-3S,5R racemate.

15 EXAMPLE 3

(E)-6-[3'-(4"-Fluorophenyl)-1'-methylindol-2'-ylethenyl]-4-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one (process e)/lactonisation; compound 4)

20 a) A solution of 1.1 g (2.87 mmol) of crude compound no. 3 in 50 ml of dry benzene is refluxed for 8 hours. The solvent is evaporated at reduced pressure, and the residue is flash chromatographed on a silica gel column utilizing 19:1 chloroform/methanol as the eluant to obtain the product as a mixture of four diastereoisomers (two cis and two trans)(compound 4).

25 b) The mixture of isomers obtained is separated by high pressure liquid chromatography using a silica gel column and, as the solvent, 7:2:1 methyl t-butyl ether/n-hexane/acetone to obtain the racemic trans compound m.p. 147-150° (compound no. 5). A subsequent batch melted at 150-154°.

30 bii) The obtained trans racemate may be resolved by conventional means into two optically pure enantiomers, the 4R,6S and 4S,6R isomers by, for example, (i) reacting with (-)- α -naphthylphenylmethychlorosilane, (ii) separating the obtained

diastereoisomeric silyloxy compounds and (iii) cleaving the silyl groups with tetra-*n*-butylammonium fluoride in a mixture of acetic acid and tetrahydrofuran, as set forth above. The amorphous solid 4*R*,6*S* enantiomer has an $[\alpha]^{25} = -18.5^\circ$ (CHCl₃, c = 0.2 g
S (compound 17). The 4*S*,6*R* enantiomer was also an amorphous solid.

c) The racemic *cis* lactone may also be isolated from the silica gel column, m.p. 48°-62°C (dec.) (compound 6). It too may be resolved by conventional means into two optically pure enantiomers. The two stereoisomers may be designated as the 4*R*,6*R* and 4*S*,6*S* isomers, the former being preferred.
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EXAMPLE 4

Methyl (+)-erythro-(E)-3,5-dihydroxy-7-[3'-(4"-fluorophenyl)-1'-(1"-methylethyl)indol-2'-yl]hept-6-enoate (compound no. 7)

a) (E)-3-[3'-(4"-Fluorophenyl)-1'-(1"-methylethyl)indol-2'-yl]-prop-2-enal (Reaction AA; compound IVc)

A solution of 50 ml (49.6 g, 0.5 mole) of 3-N,N-dimethyl-aminoacrolein in 200 ml of dry acetonitrile is slowly added over a 30 minute period to a solution of 50 ml (82.5 g, 0.5392 mole) of phosphorus oxychloride in 200 ml of dry acetonitrile stirred at -10°-0° under nitrogen. 45.3 g (0.1788 mole) of 3-(4'-Fluorophenyl-1-(1'-methylethyl)indole (XXIIAa) is added portionwise over a 2 minute period to the reaction mixture stirred at 0°-5°. The reaction mixture is refluxed for 24 hours under nitrogen, cooled to room temperature and slowly poured (over a 20 minute period) into a cold (10°) stirred mixture of 2 litres of toluene and a solution of 130 g of sodium hydroxide in 2 litres of water so that the temperature does not exceed 26°. The reaction mixture is filtered to remove the insolubles, and the toluene layer is separated and washed twice with 1 litre portions of water. The 20 additional insolubles are removed by filtration, and the toluene layer is evaporated at reduced pressure and 50°-60°. The obtained viscous oil is chromatographed on 550 g of silica gel (20-230 mesh A.S.T.M.) using methylene chloride as the eluant; twenty
25
30

100 ml fractions are collected over a 2 hour period. The fractions containing the desired product (as determined by thin layer chromatography) are combined and evaporated to dryness at reduced pressure and 50°-60° to obtain the crude solid product.

5 The crude product is dissolved in 70 ml of refluxing absolute ethanol, the obtained solution is cooled to 65°, 70 ml of n-heptane is added, and the resulting solution is cooled to -5°-0° for 15 minutes. The precipitate solids are collected by filtration, washed with 20 ml of ice cold n-heptane and vacuum dried at 50°-55° to obtain the yellow product m.p. 122°-123°. A subsequent batch melted at 129-132°.

10 3-(4'-Fluorophenyl-1-(1'-methylethyl)indole (m.p. 94.5-95°) is prepared via 4-chloroacetyl-1-fluorobenzene and N-(4-fluorobenzoylmethyl)-N-(1-methylethyl)aniline (m.p. 78-81°) in conventional manner.

15 b) Methyl (+)-(E)-7-[3'-4"-fluorophenyl]-1'-(1"-methylethyl)-indol-2'-yl]-5-hydroxy-3-oxohept-6-enoate (Reaction A; compound Vb)

Analogous to 1e) m.p. 95-97°.

20 The product is a racemate which may be resolved into its R and S components.

c) Methyl (+)-erythro-(E)-3,5-dihydroxy-7-[3'(4"-fluorophenyl)-1'-(1"-methylethyl)indol-2'yl]hept-6-enoate Process a)/
stereospecific; compound no. 7)

25 (i) 30 ml of 1M. triethylborane/tetrahydrofuran (30 mmol) is added dropwise to a solution of 12.2 g (26 mmol assuming 100% yield) of crude Compound Vb in 400 ml of dry tetrahydrofuran (distilled over lithium aluminium hydride) stirred at room temperature, 55 ml of air (at 760 mm Hg and 25°) is bubbled through over 5 minutes, and the reaction mixture is stirred at room temperature under nitrogen for 2 hours. The reaction mixture is cooled to -80°, 1.3 g (34 mmol) of sodium borohydride is added, and the reaction mixture is stirred overnight at -80°

under nitrogen. The reaction mixture is allowed to warm to -10°-0°, quenched by the dropwise addition of sufficient 2N. hydrochloric acid to lower the pH to 2 and extracted with diethyl ether. The diethyl ether extract is washed twice with saturated 5 sodium chloride solution, dried over anhydrous magnesium sulfate and evaporated at reduced pressure to a yellow oil, the crude ethylborate ester. 400 ml of anhydrous methanol is added, and the reaction mixture is stirred at room temperature for 2.5 hours. 10 The methanol is evaporated at reduced pressure and 40°, and the residue is dissolved in 4:1 (by volume) chloroform/ethyl acetate and chromatographed on a silica gel column using the same solvent as the eluant. The fractions containing the relatively pure product are combined and evaporated at reduced pressure to obtain the product as an oil.

15 (ii) An impure chromatography fraction (containing some product) is evaporated at reduced pressure, and the residue is triturated with diethyl ether and *n*-pentane and seeded with a crystal that formed upon addition of the methanol to the ethylborate ester to obtain the product (96% erythro) as a white 20 powder, m.p. 122°-124°.

The product is a racemate which may be resolved into two optically pure enantiomers, the 3R,5S and 3S,5R isomers, of which the former is preferred.

EXAMPLE 5

25 Erythro-(+)-(E)-3,5-dihydroxy-7-[3'-(4"-fluorophenyl)-1'-(1"-methylethyl)indol-2'-yl]hept-6-enoic acid (process d)/esterhydrolysis; compound no. 8

(a) 4.5 ml of 1N. sodium hydroxide solution (4.5 mmol) and 2.0 g (4.7 mmol) of Compound 7 are stirred in 150 ml of ethanol 30 at room temperature for 2 hours, the solvent is evaporated at reduced pressure, and the residue is dissolved in 50 ml of water. The aqueous solution is gently extracted with diethyl ether, the traces of ether in the aqueous layer are removed at

reduced pressure, and the aqueous layer is freeze dried to obtain the racemic product as its sodium salt (compound no. 9) m.p. 194°-197°.

(b) Compound no. 9 is dissolved in water, and the solution is acidified to pH2 with 2N. hydrochloric acid and extracted with diethyl ether. The diethyl ether extract is washed three times with saturated sodium chloride solution, dried over anhydrous magnesium sulfate and evaporated at reduced pressure to obtain the crude solid racemic free acid (compound no. 8).

Sodium salt and free acid can be resolved into their 3R,5S and 3S,5R isomers the former being preferred.

EXAMPLE 6

(E)-(+)-4-hydroxy-6-[3'-(4"-fluorophenyl)-1'-(1"-methylethyl)-indol-2'-ylethenyl]-3,4,5,6-tetrahydro-2H-pyran-2-one (process e)/catalyzed lactonisation; compound no. 10)

6.9 g of crude Compound no. 8 (which contains some threo isomer) and 7 g of N-cyclohexyl-N'-[2-(N"-methylmorpholinium)ethyl]carbodiimide p-toluenesulfonate are stirred in 300 ml of methylene chloride at room temperature for 3 hours. The reaction mixture is extracted with water, dried over anhydrous magnesium sulfate and evaporated at reduced pressure. The residual oil (containing compound no. 10) is chromatographed on a silica gel column utilizing 7:2:1 (by volume) methyl *t*-butyl ether:*n*-hexane:acetone as the eluant. The initial fractions, containing the racemic trans lactone, are combined and evaporated at reduced pressure to obtain the product as a foam (compound no. 11). Fractions containing the cis compound are evaporated at reduced pressure to obtain a solid product m.p. 170-175° (dec.) (compound no. 12).

The trans and cis products are racemates which may be resolved into their 4R,6S and 4S,6R or 4R,6R, 4S,6S isomers respectively, the former being preferred in each case.

EXAMPLE 7

Sodium erythro-(+)-(E)-3,5-dihydroxy-7-[3'-(4"-fluorophenyl)-1'-(1"-methylethyl)indol-2'-yl]hept-6-enoate (alternative method/process d)/lactone hydrolysis; compound no. 13 = cmpd. 9)

5 2.6 g of the corresponding trans lactone (cf. Ex. 6), 12.6 ml of 0.5N. sodium hydroxide solution (6.3 mmol) and 200 ml of absolute ethanol are stirred for 2 hours at room temperature, the solvent is evaporated at reduced pressure, and the residue is dissolved in 150 ml of water. The aqueous solution is gently 10 washed with diethyl ether and freeze dried to obtain the solid racemic product. This compound can be resolved into its optically pure isomers 3R,5S ($[\alpha]^{25} = -13.33^\circ$ (CHCl₃, c = 0.99 g); compound no. 14) and 3S,5R (compound no. 15) the former being preferred.

15 The 3R,5S isomer can also be obtained by the above process directly from the optically pure compound 20.

EXAMPLE 8

Sodium threo-(+)-(E)-3,5-dihydroxy-7-[3'-(4"-fluorophenyl)-1'-(1"-methylethyl)indol-2'-yl]hept-6-enoate (compound no. 16)

20 Obtained analogously to Example 7 from the corresponding cis lactone.

This compound may also be resolved into its optically pure isomers 3R,5S and 3S,5R, whereby the former is preferred.

EXAMPLE 9

25 (E)-Trans-6S-[3'-(4"-fluorophenyl-1'-methylindol-2'-ylethenyl]-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one (compound no. 17)
a) 3-(4'-Fluorophenyl)-1-methylindole-2-carboxaldehyde (Reaction R; compound no. IVd)

30 78.5 ml (0.84 mole) of phosphorus oxychloride is added dropwise over a 20 minute period to 213 ml of dimethylformamide stirred at 0° under nitrogen, the temperature of the reaction mixture not being allowed to exceed 10°. The reaction mixture is heated to 80°, a solution of 163.5 g (0.727 mole) of 3-(4'fluorophenyl)-1-methylindole in 270 ml of dimethylformamide is added at a rate such that the temperature of the reaction mixture is

maintained at 81°-83°, the reaction mixture is maintained at 80°-81° for 5 hours and cooled to 10°, and 1 litre of 15% sodium hydroxide solution is added dropwise at a rate such that the temperature of the reaction mixture is maintained at 35°-40°, the 5 reaction mixture being stirred under nitrogen throughout. The reaction mixture is cooled to 25°, and the solids are collected by filtration, washed three times with 500 ml portions of water and dissolved in 500 ml of methylene chloride. The methylene chloride solution is filtered through 500 ml of silica gel 10 (70-230 mesh A.S.T.M.) and the silica gel is carefully washed with 2 litres of methylene chloride. The methylene chloride solutions are combined and concentrated to a volume of 300 ml at reduced pressure, 300 ml of absolute ethanol is added and the reaction mixture is distilled until the internal temperature 15 reaches 78°. The reaction mixture is cooled to 0° and the precipitated bright yellow product is collected by filtration and vacuum dried at room temperature, m.p. 80.5°-81.5°.

b) 3-(4'-Fluorophenyl)-2-hydroxymethyl-1-methylindole
(Reaction S; compound XVIIIa)

20 A solution of 160 g (0.6324 mole) of Compound IVd in 650 ml of tetrahydrofuran is added over a 20 minute period to a mixture of 9.6 g (0.25 mole) of sodium borohydride, 650 ml of tetrahydrofuran and 65 ml of methanol stirred at 0° under nitrogen, the temperature of the reaction mixture not being 25 allowed to exceed 14°. The reaction mixture is stirred under nitrogen at 5°-10° for 30 minutes, and the tetrahydrofuran and methanol are distilled at atmospheric pressure. 1 litre of toluene is added to the oily residue (200-300 ml) and the residual tetrahydrofuran is distilled at atmospheric pressure 30 until the temperature reaches 108°-110°. The toluene solution is cooled to 40°, 1.3 litre of 0.5N. sodium hydroxide is rapidly added, and the two phases are mixed and separated. The organic phase is heated to 50°-55°, 1.1 litre of n-hexane is added, the

the solution is cooled to 5°, and the precipitated colourless product is collected by filtration and vacuum dried for 16 hours at room temperature, m.p. 110°-111°.

5 c) 2-Chloromethyl-3-(4'-fluorophenyl)-1-methylindole
(Reaction T; compound XXIIIa)

29.5 ml (0.404 mole) of thionyl chloride is added over a 10 minute period to a solution of 63.8 g (0.25 mole) of Compound XVIIIa in 650 ml of dry tetrahydrofuran (dried over molecular sieves) stirred at -7° under nitrogen. The reaction mixture is 10 stirred at -5°-0° under nitrogen for 2.5 hours, 350 ml to toluene is added (with cooling to keep the temperature of the reaction mixture at or below 5°, tetrahydrofuran and excess thionyl chloride are distilled at 0.5-2 mm. Hg. and 0°-10° until the volume of the reaction mixture is about 400 ml, an additional 15 350 ml of toluene is added and another 100 ml of solvent is distilled at 0.5-1 mm. Hg. and 10°-20° to obtain a solution of the product in toluene.

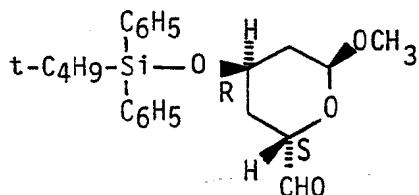
20 d) 3-(4'Fluorophenyl)-1-methyl-2-triphenylphosphonium-methylindole chloride (Reaction V; compound XXIVa)

20 A solution of 66.2 g (0.25 mole) of triphenylphosphine in 1 litre of toluene is added over a 3 minute period to the solution obtained in c), stirred at 15°-20° under nitrogen, and the reaction mixture is stirred at 108°-110° under nitrogen for 5 hours and cooled to 25°. The product is collected by filtration, 25 washed twice with 50 ml portions of toluene and once with 50 ml of n-heptane and vacuum dried, m.p. 270°-271° (dec.).

20 e) (E)-4βR-(1',1'-dimethylethyl-diphenylsilyloxy)-6αS-[3'-(4"-fluorophenyl)-1'-methylindol-2'-ylethenyl]-2β-methoxy-3,4,5,6-tetrahydro-2-pyran and the corresponding (Z) form (Reaction W; compounds XXVIa and XXVIb)

20 6.0 ml of 1.3M n-butyllithium/n-hexane (7.8 mmol) is added dropwise over a 7 minute period to a slurry of 4.0 g (7.47 mmol) of Compound XXIVa stripped from toluene at reduced pressure and

dried under high vacuum prior to use in 100 ml of dry tetrahydrofuran (freshly distilled from sodium and benzophenone) stirred at room temperature under nitrogen. The reaction mixture is cooled to 0°, and 2.98 g (7.48 mmol) of compound



(stripped from toluene at reduced pressure and dried under high vacuum prior to use) in 20 ml of dry tetrahydrofuran is added dropwise over a 5 minute period, an additional 10 ml of dry tetrahydrofuran is added, and the reaction mixture is maintained at about 0° for 45 minutes, allowed to warm to room temperature and maintained at room temperature for 17 hours, the reaction mixture being stirred under nitrogen throughout. The reaction mixture is poured into 500 ml of water and extracted four times with 250 ml portions of diethyl ether. The diethyl ether extracts are combined and dried over anhydrous magnesium sulfate and then over anhydrous sodium sulfate and evaporated at reduced pressure. The last traces of diethyl ether are removed under high vacuum to obtain a semi-solid residue. The residue is subjected to medium pressure liquid chromatography utilizing a silica gel column and methylene chloride as the eluant, with those fractions containing one product and one or more contaminants or a mixture of the products (with or without one or more contaminants) as determined by thin layer chromatography being recycled, to obtain the (E) (i.e., trans) olefin (Compound XXVIa) as an orange foam and the (Z) (i.e., cis) olefin (Compound XXVIb) also as an orange foam.

f) (E)-4βR (1',1'-dimethylethyl-diphenylsilyloxy)-6αS-[3'-(4"-fluorophenyl)-1'-methylindol-2'-ylethenyl]-2-hydroxy-3,4,5,6-tetrahydro-2H-pyran; compound XXVIIa and its 6βR isomer; compound XXVIIb (Reaction X)

5 1.18 g (1.9 mmol) of compound XXVIIa is dissolved in 56 ml of glacial acetic acid, 37.2 ml of tetrahydrouran is added, and 18.6 ml of distilled water is slowly added, the reaction mixture being stirred at room temperature throughout. The reaction mixture is stirred at 60° for 18.5 hours and allowed to cool. The ~~tetrahydrofuran~~ is evaporated at reduced pressure, and the reaction mixture is poured into 500 ml of distilled water and extracted four times with 300 ml portions of diethyl ether. The ~~diethyl ether extracts~~ are combined, washed with saturated sodium bicarbonate solution (until no gas is evolved upon shaking), dried over anhydrous magnesium sulfate and then over anhydrous sodium sulfate and evaporated to dryness at reduced pressure. The last traces of solvent are removed under high vacuum to obtain a yellow foam. Flash chromatography of the foam utilizing 250 g of silica gel and 1:1 (by volume) diethyl ether/n-hexane as the eluant yielded Compound XXVIIa and Compound XXVIIb.

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g) (E)-4βR-(1',1'dimethylethyl-diphenylsilyloxy)-6αS-[3'-(4"-fluorophenyl)-1'-methylindol-2'-ylethenyl]-3,4,5,6-tetrahydro-2H-pyran-2-one (Reaction Y; compound XXVIIa)

A solution of 236.8 mg (0.391 mmol) of compound XXVIIa in 8 ml of acetone (passed through a column of Activity I alumina immediately prior to use) is added to 137.5 mg (1.174 mmol) of N-methylmorpholine N-oxide (obtained by heating N.methylmorpholine N-oxide hydrate at 90° for 2-3 hours under high vacuum), the reaction mixture is stirred at room temperature under nitrogen until the solid dissolves, 23.5 mg (0.025 mmol) of dichlorotris(triphenylphosphine)ruthenium (II) is added, and the reaction mixture is stirred under nitrogen for 55 minutes, 10 ml of diethyl ether is added, and the resulting solid is washed

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several times with diethyl ether. The diethyl ether washings are combined, the diethyl ether is evaporated at reduced pressure to near dryness, and the residue is dissolved in 100 ml of diethyl ether. The diethyl ether solution is washed twice with 100 ml portions of ice-cold 2.5% hydrochloric acid, twice with 100 ml portions of saturated sodium bicarbonate solution and once with 100 ml of saturated sodium chloride solution, dried over anhydrous sodium sulfate and evaporated to dryness at reduced pressure to obtain the crude product as a yellow oil.

10 h) (E)-trans-6S-[3'-(4"-fluorophenyl)-1'-methylindol-2'-yl-ethenyl]-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one
(Process d)/deprotection; compound no. 17)

15 113 μ l of glacial acetic acid is added dropwise to a solution of 237.5 mg (0.391 mmol) of crude Compound XXVIIa in 18 ml of dry tetrahydrofuran stirred at room temperature under nitrogen followed by the dropwise addition of 1.564 ml of 1M. tetra-n-butylammonium fluoride/tetrahydrofuran. The reaction mixture is stirred at room temperature under nitrogen for 2 hours, poured into 200 ml of ice-cold water and extracted four times with 75 ml portions of diethyl ether. The organic phase are combined, washed once with 300 ml of saturated sodium bicarbonate solution and once with 300 ml of saturated sodium chloride solution and dried over anhydrous sodium sulfate. The solvent is evaporated at reduced pressure, with the last traces being evaporated under high vacuum to obtain a yellow oil which is triturated with diethyl ether to obtain the product as a pale yellow solid. Additional product is obtained from the mother liquor by repeating this procedure three times, m.p. 139°-140°.

20 A second batch obtained by resolution of the racemate had an $[\alpha]_D^{25} = -18.5^\circ$ (CHCl₃, c=0.2 g) [(cf. Example 3)b)ii)].

The corresponding (E), cis, 6R,4R isomer is obtained analogously (compound no. 18) starting from compound XXVIIb.

The corresponding (Z), trans, 6S,4R isomer is obtained analogously; compound no. 19

$[\alpha]_D^{25} = +136.935^\circ$ (CH_2Cl_2 , $c = 1.24$ g) starting from XXVIB.

5 EXAMPLE 10

(E)-Trans-6S-[3'-(4"-fluorophenyl)-1'-(1"-methylethyl)-indol-2'-ylethenyl]-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one (compound no. 20)

Obtained analogously to Example 9 starting from XXIIIAa and the lactone illustrated is Example 9)e).

$[\alpha]_D^{25} = -15.84^\circ$ (CHCl_3 , $c = 1.3$ g).

Compounds 1 to 20 have the following structures:

Compound no. 1: $R = 4\text{-F-C}_6\text{H}_4\text{-}$; $R_6 = \text{CH}_3$; $R_2 = R_3 = \text{H}$; $X = (\text{E})\text{CH=CH}$; $Z = \text{IIa}$; $R_6 = \text{H}$; $R_7 = \text{CH}_3$ (mixture of 4 stereoisomers).

Compound no. 2: $R = 4\text{-F-C}_6\text{H}_4\text{-}$; $R_6 = \text{CH}_3$; $R_2 = R_3 = \text{H}$; $X = (\text{E})\text{CH=CH}$; $Z = \text{IIa}$; $R_6 = \text{H}$; $R_7 = \text{K}$ (mixture of 4 stereoisomers).

Compound no. 3: $R = 4\text{-F-C}_6\text{H}_4\text{-}$; $R_6 = \text{CH}_3$; $R_2 = R_3 = \text{H}$; $X = (\text{E})\text{CH=CH}$; $Z = \text{IIa}$; $R_6 = R_7 = \text{H}$ (mixture of 4 stereoisomers).

Compound no. 4: $R = 4\text{-F-C}_6\text{H}_4\text{-}$; $R_6 = \text{CH}_3$; $R_2 = R_3 = \text{H}$; $X = (\text{E})\text{CH=CH}$; $Z = \text{IIb}$; $R_6 = \text{H}$ (mixture of 4 stereoisomers).

Compound no. 5: $R = 4\text{-F-C}_6\text{H}_4\text{-}$; $R_6 = \text{CH}_3$; $R_2 = R_3 = \text{H}$; $X = (\text{E})\text{CH=CH}$; $Z = \text{IIb}$; $R_6 = \text{H}$ (trans racemate).

Compound no. 6: $R = 4\text{-F-C}_6\text{H}_4\text{-}$; $R_6 = \text{CH}_3$; $R_2 = R_3 = \text{H}$; $X = (\text{E})\text{CH=CH}$; $Z = \text{II b}$; $R_6 = \text{H}$ (cis racemate).

Compound no. 7: $R = 4\text{-F-C}_6\text{H}_4\text{-}$; $R_6 = \text{i-C}_3\text{H}_7$; $R_2 = R_3 = \text{H}$; $X = (\text{E})\text{CH=CH}$; $Z = \text{IIa}$; $R_6 = \text{H}$; $R_7 = \text{CH}_3$ (erythro racemate).

Compound no. 8: $R = 4\text{-F-C}_6\text{H}_4\text{-}$; $R_6 = \text{i-C}_3\text{H}_7$; $R_2 = R_3 = \text{H}$; $X = (\text{E})\text{CH=CH}$; $Z = \text{IIa}$; $R_6 = R_7 = \text{H}$ (erythro racemate).

Compound no. 9 (= cmpd. no. 13): $R = 4\text{-F-C}_6\text{H}_4\text{-}$; $R_6 = \text{i-C}_3\text{H}_7$; $R_2 = R_3 = \text{H}$; $X = \text{R}_3 = \text{H}$; $X = (\text{E})\text{CH=CH}$; $Z = \text{IIa}$; $R_6 = \text{H}$; $R_7 = \text{Na}$ (erythro racemate).

Compound no. 10: $R = 4\text{-F-C}_6\text{H}_4\text{-}$; $R_6 = \text{i-C}_3\text{H}_7$; $R_2 = R_3 = \text{H}$; $X = (\text{E})\text{CH=CH}$; $Z = \text{IIb}$; $R_6 = \text{H}$ (mixture of 4 stereoisomers).

Compound no. 11: $R = 4-F-C_6H_4-$; $R_0 = i-C_3H_7$; $R_2 = R_3 = H$;
 $X = (E)CH=CH$; $Z = IIb$; $R_6 = H$ (trans racemate).

Compound no. 12: $R = 4-F-C_6H_4-$; $R_0 = i-C_3H_7$; $R_2 = R_3 = H$; $X = (E)CH=CH$; $Z = IIb$; $R_6 = H$ (cis racemate).

5 Compound no. 13 (= cmpd. no. 9).

Compound no. 14: $R = 4-F-C_6H_4-$; $R_0 = i-C_3H_7$; $R_2 = R_3 = H$; $X = (E)CH=CH$; $Z = IIa$; $R_6 = H$; $R_7 = Na$ (erythro 3R,5S isomer).

Compound no. 15; $R = 4-F-C_6H_4-$; $R_0 = i-C_3H_7$; $R_2 = R_3 = H$; $X = (E)CH=CH$; $Z = IIa$; $R_6 = H$; $R_7 = Na$ (erythro 3S,5R isomer).

10 Compound no. 16: $R = 4-F-C_6H_4-$; $R_0 = i-C_3H_7$; $R_2 = R_3 = H$; $X = (E)CH=CH$; $Z = IIa$; $R_6 = H$; $R_7 = Na$ (threo racemate).

Compound no. 17: $R = 4-F-C_6H_4-$; $R_0 = CH_3$; $R_2 = R_3 = H$; $X = (E)CH=CH$; $Z = IIb$; $R_6 = H$ (trans 6S,4R isomer).

15 Compound no. 18; $R = 4-F-C_6H_4-$; $R_0 = CH_3$; $R_2 = R_3 = H$; $X = (E)CH=CH$; $Z = IIb$; $R_6 = H$ (cis 6R,4R isomer).

Compound no. 19: $R = 4-F-C_6H_4-$; $R_0 = CH_3$; $R_2 = R_3 = H$; $X = (Z)CH=CH$; $Z = IIb$; $R_6 = H$ (trans 6S,4R isomer).

Compound no. 20: $R = 4-F-C_6H_4-$; $R_0 = i-C_3H_7$; $R_2 = R_3 = H$; $X = (E)CH=CH$; $Z = IIb$; $R_6 = H$ (trans 6S,4R isomer).

20 The compounds of the following tables may be prepared analogously to the preceding examples or according to processes set out hereinbefore.

[Abbreviations: DB = direct bond

25 DB = mixture of diastereoisomers
 (four stereoisomers)

E = erythro racemate
 (two stereoisomers)

T = threo racemate
 (two stereoisomers)]

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TABLE I

. (Compounds of type IAa: $R_6 = H$; when only one substituent or H appears in column "R₅, R_{5a}" then R_{5a} = H)

Cmpd. No.	R ₁	R ₂	R ₃	R ₄	R ₅ , R _{5a}	X	R ₇	Isomer(s)	m.p.
21	CH ₃	H	H	H	H		CH ₃	D	
22	CH ₃	H	H	H	H	"	C ₂ H ₅	D	Viscous oil
23	CH ₃	H	H	H	H	"	Na	D	
24	CH ₃	H	H	H	H	"	H	D	
25	CH ₃	H	H	H	H	"	Na	E	Amorphous solid
26	CH ₃	H	H	H	H	"	Na	T	Amorphous solid
27	CH ₃	6-OCH ₂ C ₆ H ₅	H	4-F	H	"	C ₂ H ₅	D	Solid foam
28	CH ₃	6-OCH ₂ C ₆ H ₅	H	4-F	H	"	K	D	
29	CH ₃	6-OCH ₂ C ₆ H ₅	H	4-F	H	"	Na	D	Amorphous solid
30	CH ₃	6-OCH ₂ C ₆ H ₅	H	4-F	H	"	H	D	
31	CH ₃	H	H	4-F	H	DB	CH ₃	D	
32	CH ₃	H	H	4-F	H	DB	Na	D	
33	CH ₃	H	H	4-F	H	DB	H	D	
34	CH ₃	H	H	3-CH ₃	4-CH ₃		C ₂ H ₅	D	Oil
35	CH ₃	H	H	3-CH ₃	4-CH ₃	"	K	D	
36	CH ₃	H	H	3-CH ₃	4-CH ₃	"	H	D	
37	i-C ₃ H ₇	H	H	4-F	H	"	C ₂ H ₅	D	
38	"	H	H	4-F	H	"	CH ₃	D	Viscous oil
39	"	H	H	4-F	H	"	K	D	
40	"	H	H	4-F	H	"	H	D	
41	CH ₃	4-OCH ₂ C ₆ H ₅	H	4-F	H	"	C ₂ H ₅	D	Viscous oil
42	CH ₃	4-OCH ₂ C ₆ H ₅	H	4-F	H	"	K	D	
43	CH ₃	4-OCH ₂ C ₆ H ₅	H	4-F	H	"	H	D	
44	CH ₃	H	H	3-CH ₃	5-CH ₃	"	C ₂ H ₅	D	Viscous oil
45	CH ₃	H	H	3-CH ₃	5-CH ₃	"	K	D	
46	CH ₃	H	H	3-CH ₃	5-CH ₃	"	H	D	
47	CH ₃	H	H	3-CH ₃	5-CH ₃	"	Na	E	Amorphous solid
48	CH ₃	H	H	3-CH ₃	5-CH ₃	"	Na	T	Amorphous solid

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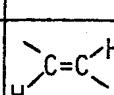
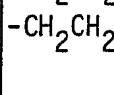
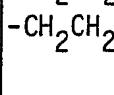
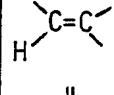
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Cmpd. No.	R ₁	R ₂	R ₃	R ₄	R ₅ , R _{5a}	X	R ₇	Isomer(s)	m.p.
49	CH ₃	5-Cl	H	4-F	H		C ₂ H ₅	D	96°-105°
50	CH ₃	5-Cl	H	4-F	H	"	K	D	
51	CH ₃	5-Cl	H	4-F	H	"	H	D	
52	CH ₃	5-OCH ₃	H	4-F	H	"	C ₂ H ₅	D	Viscous oil
53	CH ₃	H	H	4-F	H	"	Na	E	193°-196° (dec.)
54	CH ₃	7-OCH ₂ C ₆ H ₅	H	4-F	H	"	C ₂ H ₅	D	78°-82°
55	CH ₃	7-OCH ₂ C ₆ H ₅	H	4-F	H	"	Na	E	Amorphous solid
56	CH ₃	7-OCH ₂ C ₆ H ₅	H	4-F	H	"	Na	T	Amorphous solid
57	CH ₃	5-OCH ₂ C ₆ H ₅	H	4-F	H	"	C ₂ H ₅	D	Viscous oil
58	C ₆ H ₅ -CH ₂ CH ₂	H	H	4-F	H	"	CH ₃	D	Oil
59	C ₆ H ₅ -CH ₂ CH ₂	H	H	4-F	H	"	Na	E	Amorphous solid
60	C ₂ H ₅	H	H	4-F	H	"	C ₂ H ₅	D	Viscous oil
61	C ₂ H ₅	H	H	4-F	H	"	Na	E	Amorphous solid
62	C ₂ H ₅	H	H	4-F	H	"	Na	T	Amorphous solid
63	i-C ₃ H ₇	4-CH ₃	6-CH ₃	4-F	H	"	C ₂ H ₅	D	107°-110°
64	"	4-CH ₃	6-CH ₃	4-F	H	"	Na	E	Solid foam
65	"	4-CH ₃	6-CH ₃	4-F	H	"	Na	T	Solid foam
66	"	H	H	3-CH ₃	5-CH ₃	"	CH ₃	D	Viscous oil
67	"	H	H	3-CH ₃	5-CH ₃	"	Na	E	183°-186°
68	"	5-cyclohexyl	H	4-F	H	"	CH ₃	D	Viscous oil
69	"	"	H	4-F	H	"	Na	E	Solid foam
70	"	"	H	4-F	H	"	Na	T	Solid foam
71	cyclohexyl	H	H	4-F	H	"	CH ₃	D	Solid foam
72	cyclohexyl	H	H	4-F	H	"	Na	E	Amorphous solid
73	cyclohexyl	H	H	4-F	H	"	Na	T	Amorphous solid
74	i-C ₃ H ₇	6-OCH ₂ C ₆ H ₅	H	4-F	H	"	C ₂ H ₅	D	Solid foam
75	i-C ₃ H ₇	H	H	3-CH ₃	4-F, 5-CH ₃	"	C ₂ H ₅	D	Viscous oil

Cmpd. No.	R ₁	R ₂	R ₃	R ₄	R ₅ , R _{5a}	X		Isomer(s)	m.p.
76	i-C ₃ H ₇	H	H	2-CH ₃	H		Na	E	Amorphous solid
77	"	H	H	2-CH ₃	H	"	Na	T	Amorphous solid
5 78	"	H	H	3-CH ₃	4-F	"	Na	E	Amorphous solid
79	"	H	H	3-CH ₃	4-F	"	Na	T	Amorphous solid
80	"	H	H	3-CH ₃	4-F, 5-CH ₃	"	Na	E	Amorphous solid
81	"	6-0CH ₂ C ₆ H ₅	H	4-F	H	"	Na	E	180°-182° (dec.)
138	"	4-iC ₃ H ₇	6-iC ₃ H ₇	4-F	H	"	C ₂ H ₅	E	123.5-125°
10 140	i-C ₄ H ₉	H	H	4-F	H	"	Na	E	140-160° (dec.)
142	i-C ₃ H ₇	H	H	2-CH ₃	4-F	"	Na	E	155-168° (dec.)
143	"	H	H	2-CH ₃	4-F	"	CH ₃	D (mostly E)	
144	i-C ₄ H ₉	H	H	4-F	H	"	CH ₃	D (mostly E)	

TABLE II

(Compounds of type IAb: $R_6 = H$; when only one substituent or H appears in column " R_5, R_{5a} " then $R_{5a} = H$)

Cmpd. No.	R_1	R_2	R_3	R_4	$R_{5,} R_{5a}$	X	Isomer(s)	m.p.
5	82	CH_3	H	H	H		<u>cis</u>	Solid foam
	83	CH_3	H	H	H	"	<u>trans</u>	119.5-121°
	84	CH_3	6- $OCH_2C_6H_5$	H	4-F	H	"	mixture: ~ 75% <u>trans</u> ~ 25% <u>cis</u>
	85	CH_3	H	H	4-F	H		<u>cis</u>
	86	CH_3	H	H	4-F	H		<u>trans</u>
10	87	CH_3	H	H	3- CH_3	4- CH_3		<u>cis</u>
	88	CH_3	H	H	3- CH_3	4- CH_3	"	<u>trans</u>
	89	$i-C_3H_7$	4- CH_3	6- CH_3	4-F	H	"	$\geq 95\%$ <u>cis</u>
	90	"	4- CH_3	6- CH_3	4-F	H	"	150.5-151°
	91	CH_3	4- $OCH_2C_6H_5$	H	4-F	H	"	<u>cis</u>
15	92	CH_3	4- $OCH_2C_6H_5$	H	4-F	H	"	<u>trans</u>
	93	CH_3	H	H	3- CH_3	5- CH_3	"	<u>cis</u>
	94	CH_3	H	H	3- CH_3	5- CH_3	"	<u>trans</u>
	95	CH_3	5-Cl	H	4-F	H	"	<u>cis</u>
	96	CH_3	5-Cl	H	4-F	H	"	<u>trans</u>
20	97	CH_3	5- OCH_3	H	4-F	H	"	<u>cis</u>
	98	CH_3	5- OCH_3	H	4-F	H	"	<u>trans</u>
	99	CH_3	7- $OCH_2C_6H_5$	H	4-F	H	"	<u>cis</u>
	100	CH_3	7- $OCH_2C_6H_5$	H	4-F	H	"	<u>trans</u>
	101	CH_3	5- $OCH_2C_6H_5$	H	4-F	H	"	mixture: ~ 80% <u>cis</u> ~ 20% <u>trans</u>
	102	CH_3	"	H	4-F	H	"	<u>trans</u>
	103	$C_6H_5CH_2CH_2$	H	H	4-F	H	"	<u>cis</u>
	104	"	H	H	4-F	H	"	<u>trans</u>
	105	$i-C_3H_7$	H	H	3- CH_3	5- CH_3	"	<u>cis</u>
	106	"	H	H	3- CH_3	5- CH_3	"	<u>trans</u>
30	107	C_2H_5	H	H	4-F	H	"	<u>cis</u>
	108	"	H	H	4-F	H	"	<u>trans</u>
	109	$i-C_3H_7$	H	H	3- CH_3	4-F	"	<u>cis</u>

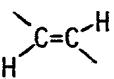
Cmpd. No.	R ₁	R ₂	R ₃	R ₄	R ₅ , R _{5a}	X	Isomer(s)	m.p.
110	i-C ₃ H ₇	H	H	3-CH ₃	4-F		<u>trans</u>	140.5-141.5°
111	"	5-cyclo-hexyl	H	4-F	H	"	<u>cis</u>	Solid foam
112	"	"	H	4-F	H	"	<u>trans</u>	162-166°
113	cyclohexyl	H	H	4-F	H	"	<u>cis</u>	Solid foam
114	"	H	H	4-F	H	"	<u>trans</u>	Solid foam
115	i-C ₃ H ₇	H	H	2-CH ₃	H	"	<u>cis</u>	Solid foam
116	"	H	H	2-CH ₃	H	"	<u>trans</u>	Solid foam
117	"	H	H	3-CH ₃	4-F, 5-CH ₃	"	mixture: ~ 88% <u>cis</u> ~ 12% <u>trans</u>	107-113°
118	"	H	H	3-CH ₃	4-F, 5-CH ₃	"	<u>trans</u>	166.5-167.5°
119	"	6-0CH ₂ C ₆ H ₅	H	4-F	H	"	<u>trans</u>	152-153° (dec.)
139	i-C ₄ H ₉	H	H	4-F	H	"	<u>trans</u>	51-55°(dec.)
141	i-C ₃ H ₇	H	H	2-CH ₃	4-F	"	<u>trans</u>	64-69°

TABLE III

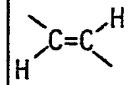
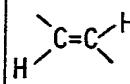
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(Compounds of type IBa; when only one substituent or H appears in column "R₅, R_{5a}" then R_{5a} = H)

Cmpd. No.	R ₁	R ₂	R ₃	R ₄	R ₅ , R _{5a}	X	R ₆	R ₇	Isomer(s)	m.p.	
5 120	CH ₃	H	H	4-F	H		H	C ₂ H ₅	D		
121	CH ₃	H	H	4-F	H	"	H	K	D		
122	CH ₃	H	H	4-F	H	"	H	H	D		
123	C ₂ H ₅	5-OCH ₃	H	3-CH ₃	H	-CH ₂ CH ₂ -	CH ₃	CH ₃	D		
124	C ₂ H ₅	5-OCH ₃	H	3-CH ₃	H	-CH ₂ CH ₂ -	CH ₃	K	D		
10 125	C ₂ H ₅	5-OCH ₃	H	3-CH ₃	H	-CH ₂ CH ₂ -	CH ₃	H	D		
126	i-C ₃ H ₇	H	H	4-F	H		H	C ₂ H ₅	D		
127	"	H	H	4-F	H	"	H	K	D		
128	"	H	H	4-F	H	"	H	H	D		
129	CH ₃	H	H	H	H	"	H	C ₂ H ₅	D	Viscous oil	

TABLE IV

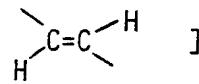
(Compounds of type IBb); when only one substituent or H appears in column "R₅, R_{5a}" then R_{5a} = H)

Cmpd. No.	R ₁	R ₂	R ₃	R ₄	R ₅ , R _{5a}	X	R ₆	Isomer(s)	m.p.
5 130	CH ₃	H	H	4-F	H		H	<u>cis</u>	
131	CH ₃	H	H	4-F	H	"	H	<u>trans</u>	
132	C ₂ H ₅	5-OCH ₃	H	3-CH ₃	H	-CH ₂ CH ₂ -	CH ₃	<u>cis</u>	
133	C ₂ H ₅	5-OCH ₃	H	3-CH ₃	H	-CH ₂ CH ₂ -	CH ₃	<u>trans</u>	
134	i-C ₃ H ₇	H	H	4-F	H		H	<u>cis</u>	
10 135	"	H	H	4-F	H	"	H	<u>trans</u>	
136	CH ₃	H	H	H	H	"	H	<u>cis</u>	Solid foam
137	CH ₃	H	H	H	H	"	H	<u>trans</u>	Viscous oil

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TABLE V

[Compounds of type IV (sub-type XX) wherein X is



]

Cmpd. No.	R	R ₀	R ₂	R ₃	m.p.
IVe	3,4-di-CH ₃ -C ₆ H ₃ -	CH ₃	H	H	97-99°
5 IVf	4-F-C ₆ H ₄ -	C ₆ H ₅ CH ₂ CH ₂ -	H	H	86-88°
IVg	4-F-C ₆ H ₄ -	i-C ₃ H ₇	5-cyclohexyl	H	162-167°
IVh	2-CH ₃ -C ₆ H ₄ -	i-C ₃ H ₇	H	H	190-193°
IVi	3,5-di-CH ₃ -C ₆ H ₅ -	CH ₃	H	H	117-118.5°
15 IVj	4-F-C ₆ H ₄ -	CH ₃	5-OCH ₃	H	137-138.5°
IVk	4-F-C ₆ H ₄ -	CH ₃	6-OCH ₂ C ₆ H ₅	H	128.5-131°
IVl	4-F-C ₆ H ₄ -	CH ₃	4-OCH ₂ C ₆ H ₅	H	162.5-164°
IVm	4-F-C ₆ H ₄ -	CH ₃	5-Cl	H	169.5-170.5°
IVn	C ₆ H ₅ -	CH ₃	H	H	141.5-142.5°
15 IVo	4-F-C ₆ H ₄ -	CH ₃	7-OCH ₂ C ₆ H ₅	H	140-141°
IVp	4-F-C ₆ H ₄	CH ₃	5-OCH ₂ C ₆ H ₅	H	124.5-125°
IVq	3-CF ₃ C ₆ H ₄ -	CH ₃	H	H	124-124.5°
IVr	4-F-C ₆ H ₄ -	C ₂ H ₅	H	H	103-105°
IVs	4-F-C ₆ H ₄ -	i-C ₃ H ₇	4-CH ₃	6-CH ₃	189-190°
20 IVt	C ₆ H ₅ -	i-C ₃ H ₇	H	H	111-112°
IVu	3,5-di-CH ₃ -4-F-C ₆ H ₂ -	i-C ₃ H ₇	H	H	114.5°-115°
IVv	4-F-C ₆ H ₄ -	i-C ₃ H ₇	6-OCH ₂ C ₆ H ₅	H	118.5-120°
IVw	4-F-C ₆ H ₄ -	i-C ₃ H ₇	4-i-C ₃ H ₇	6-i-C ₃ H ₇	162-163°
IVx	CH ₃	C ₆ H ₅ -	H	H	crude amorphous solid

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TABLE VI
(Compounds of type XXIV)

Compound No.	R	R ₀	R ₂	R ₃	γ ^θ	m.p.
XXIVb	4-F-C ₆ H ₄ -	i-C ₃ H ₇	H	H	C1 ^θ	236-239°

Each of the compounds of Tables I and III denoted by a D in the Isomer(s) column is a mixture of four stereoisomers which may be separated. The four optically pure enantiomers that may be obtained may be designated as the 3R,5R, 3S,5S, 3R,5S and 3S,5R isomers. Except in the case of compounds 123-125 preferred are the 3R,5R and 3R,5S isomers and the racemate of which each is a constituent, viz., the 3R,5R-3S,5S (threo) racemate and the 3R,5S-3S,5R (erythro) racemate, of which the latter is preferred. The preferred isomers of compounds 123-125 are the 3R,5R and 3R,5S isomers and the racemate of which is a constituent, viz., the 3R,5R-3S,5S (erythro) racemate and the 3R,5S-3S,5R (threo) racemate, of which the former is preferred. Each of the compounds of Tables I and III denoted by an E in the Isomer(s) column is the erythro racemate which may be resolved to obtain the 3R,5S and 3S,5R enantiomers by, for example, (i) lactonization, (ii) conversion to a mixture of two diastereoisomeric silyloxy compounds, (iii) chromatographic separation of the diastereoisomeric silyloxy compounds, (iv) cleavage of the silyl group and (v) hydrolysis of the obtained optically pure lactone, as set forth in more detail above. Each of the compounds of Tables I and III denoted by a T in the Isomer(s) column is the threo racemate which may be resolved by, for example, the same procedure to obtain the 3R,5R and 3S,5S enantiomers.

Each of the compounds of Tables II and IV denoted by cis in the Isomer(s) column is the cis racemate and each of the compounds of these tables denoted by trans in the isomer column is the trans racemate, cis and trans referring to the relative positions of the hydrogen atoms in the 4- and 6-positions of the lactone ring. The cis racemates of compounds 85 and 132 may be resolved to obtain the 4R,6S and 4S,6R enantiomers and each of the other cis racemates of Tables II and IV may be resolved to obtain the 4R,6R and 4S,6S enantiomers, of which the 4R,6S and 4R,6R enantiomers are preferred. The trans racemates of Compounds

86 and 133 may be resolved to obtain the 4R,6R and 4S,6S enantiomers, and each of the other trans racemates of Tables II and IV may be resolved to obtain the 4R,6S and 4S,6R enantiomers, of which the 4R,6R and 4R,6S enantiomers are preferred. The cis and trans racemates may be resolved by Steps (ii)-(iv) of the procedure outlined in the preceding paragraph.

The following data were obtained for the preceding compounds. Unless otherwise stated the data are NMR spectra measured at 200 mHz. Shifts are in ppm. relative to tetramethylsilane.

Abbreviations:

s = singlet
d = doublet
dd = doublet of a doublet
t = triplet
q = quartet
Q = quintet
m = multiplet
br = broad
bs = broad singlet
dq = doublet of a quartet
dt = doublet of a triplet

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Cmpd.no.

1 CDCl_3 : 1.5-1.9(m,2H); 2.4-2.6 (m,2H); 2.8-3.4(br.,2H : D_2O exch); 3.7(s,3H); 3.8(s,3H); 4.26(m,1H); 4.55(m,1H); 5.85-6.1(m,1H); 6.7(2d,1H); 7.05-7.55 (m,8H).

5 4 CDCl_3 : 1.6-3.0(m,5H); 3.82(2s,3H); 4.39(m,1H); 4.78(m, $\frac{1}{2}$ H: cis/ C_6 -H); 5.3(m, $\frac{1}{2}$ H: trans/ C_6 -H); 5.82-6.0(m,1H); 6.69-6.81 (2d,1H); 7.05-7.6(m,8H).

11 CDCl_3 : 1.68(d,6H); 1.75-2.05(m,3H); 2.55-2.82(m,2H); 4.38(m,1H); 4.82(q,1H); 5.25(m,1H); 5.72(q,1H); 6.75(d,1H); 7.05-7.6(m,8H);

10 13 $\text{CDCl}_3/\text{CD}_3\text{OD}$: 1.55(m,1H); 1.6(d,6H), 2.2-2.45 (m,3H); 4.08(m,1H); 4.42 (m,1H); 4.9(q,1H); 5.75(dd,1H); 6.68(d,1H); 7.0-7.2(m,4H); 7.48-7.58(m,4H).

16 D_2O : 1.05(d,6H); 1.28(m,2H); 2.18(d,2H); 3.95(m,1H); 4.2(m,1H); 4.5(m,1H); 5.4(dd,1H); 6.4(d,1H); 6.5-7.2(m,8H).

15 18 CDCl_3 : 1.71(m,1H); 2.05(m,1H); 2.31(m,1H); 2.52(dd, $J_1=17.5\text{Hz}$; $J_2=8\text{Hz}$; 1H); 2.95(dd, $J_1=17.5\text{Hz}$; $J_2=5.5\text{Hz}$; 1H); 3.85 (s,3H); 4.31(m,1H); 4.81(m,1H); 5.97(dd, $J_1=16\text{Hz}$; $J_2=6\text{Hz}$; 1H); 6.77 (d, $J=16\text{Hz}$; 1H); 7.09-7.72(m,8H).

19 CDCl_3 : 0.75(m,1H); 1.14(m,1H); 1.49(m,1H); 2.48(m,2H); 3.76(s,3H);

20 4.1(bs,1H); 5.1(m,1H); 5.89(dd, $J_1=10.5\text{Hz}$; $J_2=10\text{Hz}$; 1H); 6.7(d, $J=10.5\text{Hz}$, 1H); 7.09-7.73(m,8H).

22 CDCl_3 : 1.29(t,3H); 1.51-1.88(m,2H); 2.48(d,2H); 3.83(s,3H); 4.08-4.37(m,3H); 4.54(m,1H); 5.96(m,1H); 6.76(m,1H); 7-7.68(m,9H).

25 D_2O : 1.38-1.73(m,2H); 2.12-2.26(m,2H); 3.60(s,3H); 3.85(m,1H); 4.25 (m,1H), 5.75 (dd,1H); 6.52(d,1H); 6.96-7.50(m,9H).

26 D_2O : 1.41(t,2H); 2.20(d,2H); 3.36(s,3H); 4.0(m,1H); 4.2(m,1H); 5.66(dd,1H); 6.38(d,1H); 6.78-7.39(m,9H).

27 CDCl_3 : 1.26(t,3H); 1.68(m,2H); 2.45(d,2H); 3.69(s,3H); 4.17(q,2H); 4.25(m,1H); 4.50(m,1H); 5.10(s,2H); 5.88(m,1H); 6.65(m,1H); 7.09(t,2H); 7.44(m,9H); 7.85(d,2H).

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29		CDCl ₃ /CD ₃ OD : 1.49-1.80(m,2H); 2.17-2.44(m,2H); 3.75(s,3H); 4.09(m,1H); 4.42(m,1H); 5.13(s,2H); 5.90(dd,1H); 6.63(d,1H); 6.77-6.92(m,2H); 7.09(t,2H); 7.27-7.54(m,8H).
5	34	CDCl ₃ : 1.28(t,3H); 1.6-1.8(m,2H); 2.3(s,6H); 2.48(m,2H); 3.82(s,3H); 4.18(q,2H); 4.3(m,1H); 4.55(m,1H); 6.0(m,1H); 6.75(2d,1H); 7.05-7.65(m,7H).
	38	CDCl ₃ : 1.45-1.82(m,2H); 1.68(d,6H); 2.48(m,2H); 3.22(d,1H, exchangeable); 3.59(m,1H, exchangeable), 3.75(s,3H); 4.2(m,1H); 4.5 (m,1H); 4.86(q,1H); 5.75(m,1H); 6.72(2d,1H); 7.05-7.55(m,8H).
10	41	CDCl ₃ : 1.28(t,3H); 1.61(m,2H); 2.42(m,2H); 3.80(s,3H); 4.13(q,2H); 4.45(bs,1H); 4.96(s,2H); 5.72(m,1H); 6.56(m,1H); 6.90(m,5H); 7.24(m,7H).
15	44	CDCl ₃ : 1.5-1.85(m,2H); 1.27(t,3H); 2.35(s,6H); 2.43-2.5(m,2H); 3.79(s,3H); 4.28(m,1H), 4.53(m,1H); 5.97(m,1H); 6.73(m,1H); 6.94-7.35(m,5H); 7.62(d,2H).
	47	D ₂ O : 1.86(s,6H); 3.18(s,3H).
	48	D ₂ O : 2.10(s,6H); 3.48(s,3H).
20	52	CDCl ₃ : 1.28(t,3H); 1.70(m,2H); 2.46(d,2H); 3.78(s,3H); 3.81(s,3H); 4.19(q,2H); 4.24(bs,1H); 5.89(m,1H); 6.68(m,1H); 6.94(m,2H); 7.17(m,3H); 7.41(m,2H).
	55	CDCl ₃ /CD ₃ OD : 1.42-1.73(m,2H); 2.12-2.42(m,2H); 4.07(s,3H); 4.40(m,1H); 5.2(s,2H); 5.83(dd,1H); 6.53-6.75(m,2H); 6.89-7.14 (m,3H); 7.27-7.50(m,8H).
25	56	CDCl ₃ /CD ₃ OD : 1.41-1.67(m,2H); 2.20-2.33(m,2H); 4.03(s,3H); 3.98-4.18(m,1H); 4.33(m,1H); 5.15(s,2H); 5.83(dd,1H); 6.59-6.73 (m,2H); 6.85-7.13(m,4H); 7.24-7.50(m,6H).
	57	CDCl ₃ : 1.28(t,3H); 1.51-1.87(m,2H); 2.37-2.62(m,2H); 3.75(s,3H); 4.08-4.33(m,3H); 4.52(m,1H); 5.02(s,2H); 5.90(m,1H); 6.57-6.73 (m,1H); 6.92-7.47(m,12H).
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Cmpd.no.

58 CDCl_3 : 1.4-1.8(m,2H); 2.45(m,2H); 2.84(m,1H, exchangeable); 3.1(t,2H); 3.45(m,1H, exchangeable); 3.72(s,3H); 4.2(m,1H); 4.42(t,2H); 5.72(m,1H); 6.4(d,1H); 7-7.55(m,13H).

5 59 $\text{CDCl}_3/\text{CD}_3\text{OD}$: 1.48(m,1H); 2.25(m,3H); 2.92(m,2H); 4.2(m,4H); 5.75(dd,1H); 6.45(d,1H); 6.9-7.5(m,13H).

60 CDCl_3 : 1.27(t,3H); 1.40(t,3H); ~ 1.40-1.85(m,2H); 2.33-2.61 (m,2H); 4.03-4.35(m,5H); 4.53(m,1H); 5.89(m,1H); 6.60-6.78 (m,1H); 7.0-7.57(m,8H).

10 61 $\text{CDCl}_3/\text{CD}_3\text{OD}$: 1.16-1.74(m,5H); 2.12-2.47(m,2H); 4.12(m,1H); 4.27(q,2H); 4.41(m,1H); 5.88(dd,1H); 6.65(d,1H); 7.0-7.56(m,8H);

62 CDCl_3 : 1.40(t,3H); 1.50-1.68(m,2H); 2.19-2.38(m,2H); 4.12(m,1H); 4.28(q,2H); 4.47(m,1H); 5.90(dd,1H); 6.67(d,1H); 7.0-7.54(m,8H).

15 64 $\text{CDCl}_3/\text{CD}_3\text{OD}$: 1.15-1.6(m,2H); 1.65(d,6H); 2.01(s,3H); 2.1-2.4 (m,2H); 2.45(s,3H); 3.92(m,1H); 4.29(m,1H); 4.84(m,1H); 5.58 (dd,1H); 6.52(d,1H); 6.60(s,1H); 6.96-7.37(m,5H).

65 $\text{CDCl}_3/\text{CD}_3\text{OD}$: 1.3-1.65(m,2H); 1.67(d,6H); 2.01(s,3H); 2.15-2.35 (m,2H); 2.43(s,3H); 3.98(m,1H); 4.34(m,1H); 4.85(m,1H); 5.54 (dd,1H); 6.53(d,1H); 6.61(s,1H); 6.95-7.38(m,5H).

20 66 CDCl_3 : 1.55(m,2H); 1.65(d,6H); 2.33(s,6H); 2.45(m,2H); 3.72 (s,1H); 4.20(m,1H); 4.50 (m,1H); 4.85(q,1H); 5.75(dd,1H); 6.7(dd,1H); 6.9-7.6(m,7H).

68 CDCl_3 : 1.1-1.6(m,7H); 1.62(d,6H); 1.62-1.94(m,5H); 2.4-2.62 (m,3H); 3.0-3.6(br,2H); 3.75(s,3H); 4.15(m,1H); 4.5(m,1H); 4.82 (q,1H); 5.6-5.8(m,1H); 6.7(d,1H); 7.05-7.45(m,7H).

25 69 $\text{CDCl}_3/\text{CD}_3\text{OD}$: 1.15-1.6(m,7H); 1.65(d,6H); 1.7-1.95(m,5H); 2.15-2.44(m,2H); 2-48-2.62(m,1H); 4.04(m,1H); 4.38(m,1H); 4.85(q1H); 5.7(dd,1H); 6.65(d,1H); 7.0-7.15(m,3H); 7.3-7.5(m,4H).

Cmpd.no.

70 $\text{CDCl}_3/\text{CD}_3\text{OD}$: 1.15-1.6(m,8H); 1.64(d,6H); 1.7-2(m,4H); 2.3(m,2H);
2.55(m,1H); 4.1(m,1H); 4.46(m,1H); 4.85(Q,1H); 5.72(dd,1H);
6.65(d,1H); 7.1(m,3H); 7.4(m,4H);

5 71 CDCl_3 : 1.3-2.05(m,11H); 2.2-2.5(m,3H); 3.1-3.6(br,2H); 3.72
(s,3H); 4.05-4.6(m,3H); 5.7(m,1H); 6.7(m,1H); 7.0-7.6(m,8H).

72 $\text{CDCl}_3/\text{CD}_3\text{OD}$: 1.5(m,4H); 1.95(m,6H); 2.3(m,4H); 4.1(m,1H);
5.72(dd,1H); 6.7(d,1H); 7.1(m,4H); 7.5(m,4H).

10 73 $\text{CDCl}_3/\text{CD}_3\text{OD}$: 1.2-1.62(m,5H); 1.74-2.05(m,5H); 2.18-2.46(m,4H);
4.14(m,1H); 4.46(m,1H); 5.75(dd,1H); 6.68(d,1H); 7.0-7.2(m,4H);
7.3-7.6(m,4H).

15 74 CDCl_3 : 1.3(t,3H); 1.4-1.82(m,2H); 1.60(d,6H); 2.38-2.58(m,2H);
4.20(q,2H); 4.50(m,1H); 4.78(m,1H); 5.13(s,2H); 5.55-5.78(m,1H);
6.57-6.74(m,2H); 6.83(d,1H); 6.98-7.14(m,3H); 7.24-7.55(m,8H).

20 75 CDCl_3 : 1.28(t,3H); 1.41-1.81(m,2H); 1.64(d,6H); 2.25-3.58(m,2H);
2.27(s,6H); 4.18(q,2H); 4.52(m,1H); 4.83(m,1H); 5.62-5.84(m,1H);
6.61-6.76(m,1H); 6.98-7.23(m,4H); 7.43-7.56(m,2H).

25 76 $\text{CDCl}_3/\text{CD}_3\text{OD}$: 1.3(m,1H); 1.5(m,1H); 1.7(d,6H); 2.1(d,3H); 2.22(m,2H);
3.9(m,1H); 4.3(m,1H); 4.9(Q,1H); 5.55(dt,1H); 6.65(d,1H);
6.95-7.55(m,8H).

77 $\text{CDCl}_3/\text{CD}_3\text{OD}$: 1.3-1.6(m,2H); 1.7(d,6H); 2.1(d,3H); 2.24(m,2H);
3.96(m,1H); 4.35(m,1H); 4.9(Q,1H); 5.58(dd,1H); 6.68(d,1H);
7.0-7.5(m,8H).

25 78 $\text{CDCl}_3/\text{CD}_3\text{OD}$: 1.45-1.81(m,2H); 1.57(d,6H); 2.15-2.46(m,2H);
2.30(s,3H); 4.88(m,1H); 5.73(dd,1H); 6.68(d,1H); 6.-95-7.70
(m,7H).

79 $\text{CDCl}_3/\text{CD}_3\text{OD}$: 1.42-1.62(m,2H); 1.68(d,6H); 2.17-2.35(m,5H);
4.1(m,1H); 4.45(m,1H); 4.90(m,1H); 5.78(dd,1H); 6.70(d,1H);
6.95-7.58(m,7H).

Cmpd. no.

80 $\text{CDCl}_3/\text{CD}_3\text{OD}$: 1.4-1.65(m,2H); 1.67(d,6H); 2.28(d,6H);
 2.12-2.45(m,2H); 4.43(m,1H); 4.88(m,1H); 5.74(dd,1H);
 6.67(d,1H); 6.98-7.22(m,4H); 7.53(d,2H).

5 82 CDCl_3 : 1.61-3.0(m,5H); 3.87(s,3H); 4.29(m,1H); 4.79(m,1H);
 5.98(dd,1H); 6.80(d,1H); 7.13(t,1H); 7.24-7.5(m,7H); 7.62(d,1H).

87 88 CDCl_3 : 1.58(s,1H); 1.82(m,1H); 1.9(m,1H); 2.35(s,6H); 2.5(q,1H);
 2.95(q,1H); 3.85(s,3H); 4.3(m,1H); 4.8(m,1H); 6.0(q,1H);
 6.8(d,1H); 7.05-7.65(m,7H).

10 88 CDCl_3 : 1.6(s,1H); 1.8-2.1(m,2H); 2.35(s,6H); 2.7(m,2H);
 3.85(s,3H); 4.38(m,1H); 5.3(m,1H); 6.0(q,1H); 6.8(d,1H);
 7.05-7.65(m,7H).

93 CDCl_3 : 1.65-2.1(m,2H); 2.52-2.8(m,2H); 2.38(s,6H); 3.85(s,3H);
 4.80(m,1H); 5.98(m,1H); 6.79(d,1H); 6.93-7.38(m,6H); 7.62(d,1H).

94 CDCl_3 : 1.3-3.0(m,4H); 2.38(s,6H); 3.82(s,3H); 5.30(m,1H);
 5.95(dd,1H); 6.78(d,1H); 6.93-7.40(m,6H); 7.62(d,1H).

97 CDCl_3 : 1.61-3.02(m,5H); 3.83(s,3H); 4.31(m,1H); 4.78(m,1H);
 5.90(dd,1H); 6.73(d,1H); 6.94(m,2H); 7.1-7.38(m,3H); 7.40(m,2H).

103 103 CDCl_3 : 1.55(m,1H); 2.18(m,1H); 2.28(s,1H); 2.46(q,1H); 2.9(q,1H);
 3.06(t,2H); 4.22(m,1H); 4.4(t,2H); 4.6(m,1H); 5.68(dd,1H);
 6.4(d,1H); 7.05-7.55(m,13H).

20 104 CDCl_3 : 1.55-1.95(m,2H); 2.42(s,1H, exchangeable); 2.65(m,2H);
 3.05(t,2H); 4.3(m,1H); 4.4(t,2H); 5.15(m,1H); 5.68(dd,1H);
 6.4(d,1H); 7.05-7.55(m,13H).

25 111 CDCl_3 : 1.1-1.35(m,5H); 1.65(d,6H); 1.65-2.0(m,5H); 2.05-2.3
 (m,2H); 2.4-2.6(m,2H); 2.92(dd,1H); 4.25(m,1H); 4.78(m,2H);
 5.65(dd,1H); 6.72(d,1H); 7.02-7.48(m,7H).

113 113 CDCl_3 : 1.2-2.55(m,14H); 2.92(q,1H); 4.3(m,2H); 4.78(m,1H);
 5.68(dd,1H); 6.75(d,1H); 7.0-7.6(m,8H).

30 114 CDCl_3 : 1.2-2.05(m,10H); 2.2-2.45(m,2H); 2.7(m,2H); 4.3(m,2H);
 5.25(m,1H); 5.65(dd,1H); 6.72(d,1H); 7.0-7.6(m,8H).

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115 CDCl_3 : 1.3-1.52(m,2H); 1.7(d,6H); 1.8(m,1H, exchangeable);
2.1(d,3H); 2.48(dd,1H); 2.9(dd,1H); 4.2(m,1H); 4.68(m,1H);
4.82(Q,1H); 5.5(m,1H); 6.7(d,1H); 7.0-7.5(m,8H).

5 116 CDCl_3 : 1.68-1.9(m,9H); 2.1(s,3H); 2.64(dq,2H); 4.18(m,1H);
4.85(Q,1H); 5.16(m,1H); 5.45(dt,1H); 6.7(d,1H); 7.0-7.5(m,8H).

129 CDCl_3 : 1.28(t,3H); 1.50-1.83(m,2H); 2.45(d,2H); 4.11-4.32(m,3H);
4.47(m,1H); 5.75(m,1H); 6.52(m,1H); 7.02-7.62(m,9H).

136 CDCl_3 : 1.55-2.97(m,5H); 2.48(s,3H); 4.24(m,1H); 4.70(s,1H);
5.72(dd,1H); 6.57(d,1H); 7.04-7.63(m,9H).

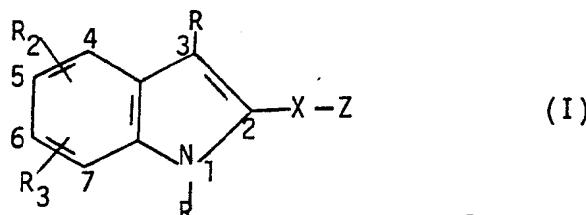
10 137 (CDCl_3) : 1.18-2.08(m,3H); 2.5(s,3H); 2.53-2.82(m,2H); 4.38
(m,1H); 5.21(m,1H); 5.72(m,1H); 6.58(d,1H); 7.07-7.65(m,9H).

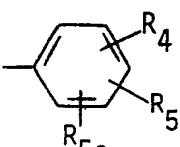
143 CDCl_3 : 1.42(m,2H); 1.66(d,6H); 2.09(d,3H); 2.42(d,2H);
3.72(s,3H); 4.05(m,1H); 4.39(m,1H); 4.84(Q,1H); 5.48(dd,1H);
6.67(d,1H); 6.90-7.56(m,7H).

15 144 CDCl_3 : 0.95(d,6H); 1.57(m,2H); 2.25(Q,1H); 2.48(d,2H); 3.74(s,3H);
4.01(d,2H); 4.22(m,1H); 4.48(m,1H); 5.78(dd,1H); 6.67(d,1H);
7.04-7.51(m,8H).

Claims:

1. Compounds of formula I



wherein one of R and R₀ is  and the other is

primary or secondary C₁-6alkyl, C₃-6cycloalkyl or phenyl-(CH₂)_m-,

wherein R₄ is hydrogen, C₁-4alkyl, C₁-4alkoxy, (except t-butoxy), trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy,

R₅ is hydrogen, C₁-3alkyl, C₁-3alkoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy,

R_{5a} is hydrogen, C₁-2alkyl, C₁-2alkoxy, fluoro or chloro, and

m is 1, 2 or 3,

with the provisos that both R₅ and R_{5a} must be hydrogen when R₄ is hydrogen, R_{5a} must be hydrogen when R₅ is

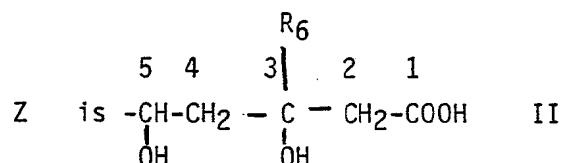
hydrogen, not more than one of R₄ and R₅ is trifluoromethyl, not more than one of R₄ and R₅ is phenoxy and not more than one of R₄ and R₅ is benzyloxy,

R₂ is hydrogen, C₁₋₄alkyl, C₃₋₆cycloalkyl, C₁₋₄alkoxy, (except t-butoxy), trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy,

5 R₃ is hydrogen, C₁₋₃alkyl, C₁₋₃alkoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy, with the provisos that R₃ must be hydrogen when R₂ is hydrogen, not more than one of R₂ and R₃ is trifluoromethyl, not more than one of R₂ and R₃ is phenoxy, and not more than one of R₂ and R₃ is benzyloxy,

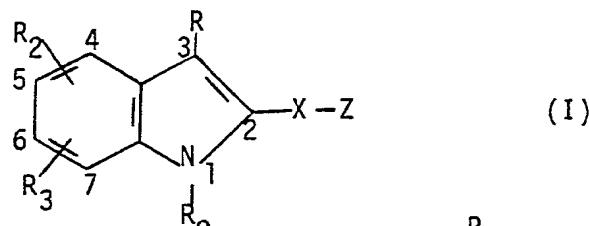
10 X is -(CH₂)_n- or -CH=CH- (n=0, 1, 2 or 3),

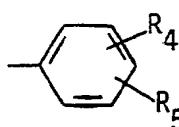
15



wherein R₆ is hydrogen or C₁₋₃alkyl in free acid form or in the form of a physiologically-hydrolysable and -acceptable ester or a δ -lactone thereof or in salt form.

20 2. A compound according to Claim 1, wherein



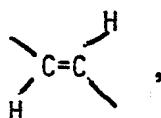
wherein one of R and R₀ is  and the other is

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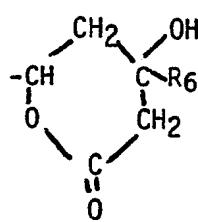
5 C_1 -3alkyl, n-butyl or i-butyl,
 wherein R_4 is hydrogen, C_1 -3alkyl, n-butyl,
 i-butyl, C_1 -3alkoxy, n-butoxy,
 i-butoxy, trifluoromethyl, fluoro,
 chloro, phenoxy or benzyloxy, and
 10 R_5 is hydrogen, C_1 -3alkyl, C_1 -3alkoxy,
 trifluoromethyl, fluoro, chloro,
 phenoxy, or benzyloxy,
 with the provisos that not more
 than one of R_4 and R_5 is trifluoro-
 methyl, not more than one of R_4 and
 R_5 is phenoxy, and not more than
 one of R_4 and R_5 is benzyloxy,

15 R_2 is hydrogen, C_1 -3alkyl, n-butyl, i-butyl,
 C_1 -3alkoxy, n-butoxy, i-butoxy, trifluoro-
 methyl, fluoro, chloro, phenoxy or benzyloxy,
 R_3 is hydrogen, C_1 -3alkyl, C_1 -3alkoxy, trifluoro-
 methyl, fluoro, chloro, phenoxy or benzyloxy,
 with the provisos that not more than one of R_2
 20 and R_3 is trifluoromethyl, not more than one
 of R_2 and R_3 is phenoxy, and not more than one
 of R_2 and R_3 is benzyloxy,

25 X is $-(CH_2)_n-$ or 

wherein n is 0, 1, 2 or 3, and

Z is $-CH_2-CH_2-C(OH)_2-CH_2-COOR_7'$ or



wherein R₆ is hydrogen or C₁-3alkyl, and
R_{7'} is hydrogen, C₁-3alkyl, n-butyl,
i-butyl, t-butyl, benzyl or M,
wherein M is a pharmaceutically
acceptable cation.

5

3. A compound according to Claim 1, wherein R is p-fluoro-phenyl, R₀ is isopropyl, R₂ and R₃ are hydrogen, X is (E)CH=CH, R₆ is hydrogen in erythro form and 3R,5S configuration and in the form of its sodium salt.

10

4. A pharmaceutical composition comprising a compound according to Claim 1 in free acid form or in the form of a physiologically-hydrolysable and -acceptable ester or a lactone thereof or in pharmaceutically acceptable salt form, together with a pharmaceutically acceptable diluent or carrier.

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5. The use of a compound according to Claim 1 in free acid form or in the form of a physiologically-hydrolysable and -acceptable ester or a lactone thereof or in pharmaceutically acceptable salt form in inhibiting cholesterol biosynthesis or treating atherosclerosis.

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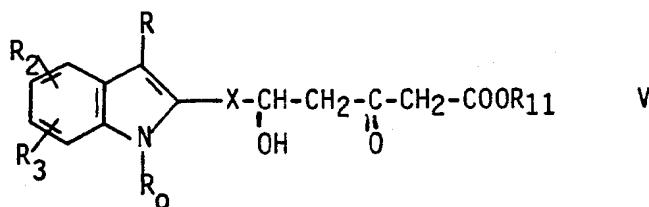
6. A compound according to Claim 1 in free acid form or in the form of a physiologically-hydrolysable and -acceptable ester or a lactone thereof or in pharmaceutically acceptable salt form for use as a pharmaceutical.

25

7. A compound according to Claim 1 in free acid form or in the form of a physiologically-hydrolysable and -acceptable ester or a lactone thereof or in pharmaceutically acceptable salt form for use in inhibiting cholesterol biosynthesis or treating atherosclerosis.

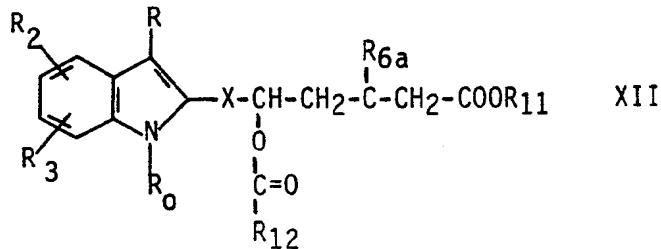
8. A process for preparing a compound according to Claim 1 which comprises

a) when R_6 is hydrogen, reducing a compound of formula V



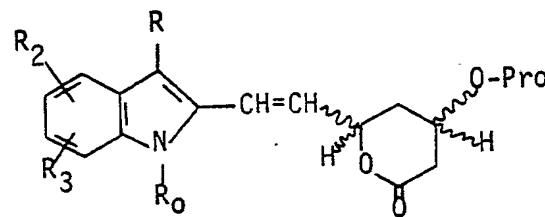
5 wherein R_{11} is a radical forming a physiologically-hydroly-sable and -acceptable ester and X, R, R_0 , R_2 and R_3 are as defined above,

b) when $R_6 = C_{1-3}$ alkyl, hydrolysing a compound of formula XII



wherein R_{6a} is C_{1-3} alkyl, R_{12} is an ester forming group and X, R, R_0 , R_3 and R_{11} are as defined above,

10 c) when X is $-CH=CH-$ deprotecting a compound of formula XXVIII



XXVIII

wherein Pro is a protecting group and R, R₀, R₂ and R₃ are as defined above,

- d) hydrolysing a compound of formula I in the form of a physiologically-hydrolysable ester or a lactone or
- 5 e) esterifying or lactonising a compound of formula I in free acid form,

and when a free carboxyl group is present, recovering the compound obtained in free form or in the form of a salt.

9. A compound of formula V, X, XI, XII, XX, XXA, XXIV, XXVI-XXVIII and XXIXB-XXIXD as hereinbefore defined.

10. A compound according to Claim 1 or 9 or a process according to Claim 8 substantially as hereinbefore described with reference to Examples 1 to 10 and Tables I to VI.



European Patent
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EUROPEAN SEARCH REPORT

0114027

Application number

EP 83 81 0548

DOCUMENTS CONSIDERED TO BE RELEVANT		Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 3)
Category	Citation of document with indication, where appropriate, of relevant passages		
D, A	<p>TETRAHEDRON LETTERS, vol. 23, no. 42, 1982, Pergamon Press, Oxford, GB</p> <p>YUH-LIN YANG et al.: "Mevinic acids and analogues: preparation of a key chiral intermediate" * Pages 4305, 4308 *</p> <p>-----</p>	1	<p>C 07 D 209/18 C 07 D 405/04 A 61 K 31/405</p>
			TECHNICAL FIELDS SEARCHED (Int. Cl. 3)
			<p>C 07 D 209/00 C 07 D 405/00</p>
<p>The present search report has been drawn up for all claims</p>			
Place of search	Date of completion of the search	Examiner	
THE HAGUE	07-03-1984	MAISONNEUVE J. A.	
CATEGORY OF CITED DOCUMENTS			
<p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p>		<p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document</p>	